Longitudinal assessment of nutritional status and its effects on the outcome of children completed treatment for Acute Lymphoblastic Leukaemia

Dr. Magdalenal R

Department of Child Health

Christian Medical College, Vellore.

DEPARTMENT OF CHILD HEALTH

CHRISTIAN MEDICAL COLLEGE & HOSPITAL

VELLORE

This is to certify that the dissertation titled “Longitudinal assessment of nutritional status and its effects on the outcome of children completed treatment for Acute Lymphoblastic Leukaemia” is a bonafide record work done by Dr.Magdalenal.R, post graduate resident in the Department of Child Health (2013-2015) at the Christian Medical College, Vellore, towards the fulfilment for the MD Paediatrics –final Examination to be held in April 2015.

Signature of the Head of the Department

Dr. Anna Simon MD, D.Ch.

Professor and Head,

Christian Medical College,

Vellore.

DEPARTMENT OF CHILD HEALTH

CHRISTIAN MEDICAL COLLEGE & HOSPITAL

VELLORE

This is to certify that the dissertation titled "Longitudinal assessment of nutritional status and its effects on the outcome of children completed treatment for Acute Lymphoblastic Leukaemia" is a bonafide record work done by Dr. Magdalenal .R, post graduate resident in the Department of Child Health(2013-2015) at Christian Medical College, Vellore, under my guidance, towards the fulfilment for the MD Paediatrics-final Examination to be held in April 2015.

Signature of the Guide

Dr. Leni Grace Mathew MD,D.Ch. MRCPCH

Professor,

Department of Child Health,

Christian Medical College,

Vellore.

ACKNOWLEDGEMENTS

First and foremost, I am grateful to GOD the Almighty for his abundant Grace that has sustained me through out and has blessed the work of my hands.

I express my gratitude and respect to my teacher and guide, Dr Leni Grace Mathew for her guidance and encouragement.

I express my gratitude to my co-guides Dr.Sarah Mathai, Dr. Narendra Chaudhary and Dr. Deepthi Boddu for their guidance, personal involvement and assistance at each point of time during the study.

I express my sincere thanks to Dr. B Antonisamy, Professor of Biostatistics for his valuable time and guidance in this study.

My sincere thanks to our nurses Nalini, Mala and Hema, office staff Mr.Sampath and project staffs Mr.Bala and Miss.Sangeetha for their constant encouragement and support during this study.

I am thankful to all the children and parents who were involved in the study, without whom, this would have not been possible.

I owe my greatest debt of gratitude to my husband, my son, my parents and my family members for their constant love and support during the study.

Dr. Magdalenal

CONTENTS

Longitudinal assessment of nutritional status and its effects on the outcome of children completed treatment for Acute Lymphoblastic Leukaemia

Magdalenal R, Sarah M, Narendra C, Deepthi B, Leni G Mathew.

Introduction:

The event free survival of children with acute lymphoblastic leukaemia (ALL) has increased substantially in the last two decades. Several authors have published the potential impact of nutritional status on the treatment outcome. Studies have shown that both under-nutrition and obesity affects the outcome in children with ALL.

A high prevalence of obesity has also been increasingly recognized in survivors of paediatric ALL. Paediatric cancer survivors have increased risk of obesity, hypertension, dyslipidaemia, and type 2 diabetes, leading to premature cardiovascular disease (CVD).

Key words:

ALL, Malnutrition, outcome, obesity in survivors, metabolic syndrome

Objectives:

1) To assess the nutritional status of children with ALL at diagnosis and at two points during treatment (i.e starting of delayed intensification and maintenance), end of treatment and annually after completion of treatment.

2) To study the impact of nutritional status on various outcome parameters such as early response to treatment, time taken for induction remission, number of febrile neutropenia episodes, relapse and death.

3) To study the prevalence of overweight and obesity in children with ALL on follow up after completion of therapy.

4) To study the prevalence of hypertension, dyslipidaemia and glucose intolerance among overweight and obese children with ALL after completion of therapy.

Materials and Methods:

Data from medical records of 241 children with ALL was retrieved during the study period. Patient's demography, risk stratification, treatment received, complications, outcome and follow up visit information were collected .Weight and height were available at diagnosis, during treatment, at the beginning of delayed intensification and maintenance phase as well as at end of treatment. BMI was calculated and only 227 children were grouped according to nutritional status as 14 children were less than 2 years of age at diagnosis. 34 children died and 195 completed treatment.The change in the nutritional status was analysed throughout treatment and post treatment during follow up. Treatment outcome was also compared between the nutritional groups. Children who were overweight/obese on follow up were further evaluated for early signs of metabolic syndrome.

Results:

241 children treated for Acute Lymphoblastic Leukaemia (ALL) were included in this study on longitudinal assessment of nutritional status from diagnosis, through treatment and post treatment period using BMI charts.

At diagnosis, 44% of children were under nourished, 47 % were well nourished and 9% were overweight/ obese. At end of treatment 13% were undernourished and 29% were obese. While there was a significant reduction in the number of children in the under nourished group, the proportion of obese children increased significantly from 7% at diagnosis to 29% at the end of treatment. This was statistically significant ($p<0.05$). The impact of nutritional status on treatment response and outcome did not show statistical significance.

114 children were reviewed during this study period; 30(26%) overweight/obese children were identified. This group was further screened for metabolic syndrome. The prevalence of hypertension was 13%, dyslipidaemia was 27% and glucose intolerance was 7% in the above study group.

Conclusion:

Nutritional status of children treated for ALL change from diagnosis, through treatment and post treatment period. In our study, it was noted that the prevalence of under nutrition reduced considerably as they went through treatment. Also significant proportion of well-nourished children became obese by the end of their treatment. In this group of obese/overweight children many had hypertension, dyslipidaemia and glucose intolerance. Hence nutritional status of children on

treatment for acute lymphoblastic leukaemia be monitored closely during and after treatment. Early signs of metabolic syndrome should be addressed and lifestyle modification should be suggested.

INTRODUCTION

Successive international clinical trials and improvement in supportive care has led to substantial improvement in the event free survival of children with acute lymphoblastic leukaemia (ALL) in the last few decades. There is increasing focus on better risk stratification, decreasing toxicity of treatment by reducing treatment for good risk patients, early identification and management of late effects of treatment.

Though nutritional status of a child at diagnosis is not a criterion for risk stratification, several authors have published its potential impact on the treatment outcome. Studies have shown that both under-nutrition and obesity affects the outcome in children with ALL. The various adverse effects of malnutrition[1-6] have been delayed remission induction, increased risk of infection leading to prolonged hospital stay and cost, increased risk of relapse, decreased tolerance to chemotherapy, increased toxicity and reduced event free survival (EFS).

There is also continued effect of the treatment in survivors leading to obesity and subsequently to metabolic syndrome. These are due to multifactorial reasons like anti-neoplastic drugs, steroids and radiation.

Our study has looked at the nutritional status of children with ALL at diagnosis and two time points during treatment (at the start of delayed intensification and maintenance), end of treatment and annually after completion of treatment. Outcome variables analysed in this study included early response to treatment, time taken for induction remission, number of febrile neutropenia episodes, relapses and death. Children who were on follow up during the study period were assessed for their nutritional status. Those who were overweight/ obese were further evaluated for early signs of metabolic syndrome.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

1) To assess the nutritional status of children with ALL at diagnosis and at two points during treatment (i.e starting of delayed intensification and maintenance), end of treatment and annually after completion of treatment

2) To study the impact of nutritional status on various outcome parameters such as early response to treatment, time taken for induction remission, number of febrile neutropenia episodes, relapse and death.

3) To study the prevalence of overweight and obesity in children with ALL on follow up after completion of therapy.

4) To study the prevalence of hypertension, dyslipidaemia and glucose intolerance among overweight and obese children with ALL after completion of therapy.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Acute Lymphoblastic Leukaemia (ALL) is the most common cancer in children and it accounts for 25% of all childhood malignancies[4].Survival rates of ALL has improved dramatically since 1980. Improvement in risk stratification strategies, large clinical trials and good supportive care has led to the success story of ALL. The significance of nutritional status in children with ALL is related to its possible influence on the course of the disease, tolerance of chemotherapy, infection rates, clinical outcome and survival. Malnutrition is a well- known health problem in our country. The outcome of treatment in ALL depends not only on the biological diversity of the leukemic cells but also on the individual variability of drug metabolism and the nutritional status of the child at presentation and it has been noticed that both under-nutrition and obesity have adverse effects on the treatment outcome of children with ALL.

Relevance of Nutritional status in children with ALL

On an average, the prevalence of under-nutrition in ALL at diagnosis is 50% in developing countries[8,9] and the prevalence of obesity at diagnosis is 8.6%[6].

Children, cancer and nutrition form a dynamic triangle. Impact of malnutrition in ALL children is multifactorial. The important aspect is the identification of a risk factor that is amenable to intervention. In contrast to most of the prognostic factors, weight is an important factor that can be modified by interventions. The importance of nutritional status in children with cancer is due to its possible influence on the course of the disease and survival. Some have attributed it to decreased tolerance of chemotherapy, altered metabolism of anti-neoplastic agents and high infection rates in malnourished children[8].

In children who are malnourished at diagnosis, it was found that chemotherapy is more toxic and less effective compared to those found with adequate nutritional status[11]. Under-nutrition is negatively associated with therapy related toxicities.

The adverse effect of under-nutrition on treatment is a result of changes that include difference in drug absorption, transportation and decreased hepatic metabolism due to lack of enzymatic activity by cytochrome P 450[11].

The increased susceptibility to infections is related to the dysfunction of the immune status in these patients. Adipose tissue plays an important role as a facilitator in the pharmacokinetics of anti-neoplastic drugs. This tissue is structurally and functionally altered in malnutrition. This decreases the effectiveness of anti-neoplastic drugs and increases the toxicity-both of which are deleterious to the children during the course of treatment.[12] The effect on malnutrition on Event free survival (EFS) is also probably due to pharmacokinetic variations which in turn has an impact on the pharmacodynamics of the drugs.

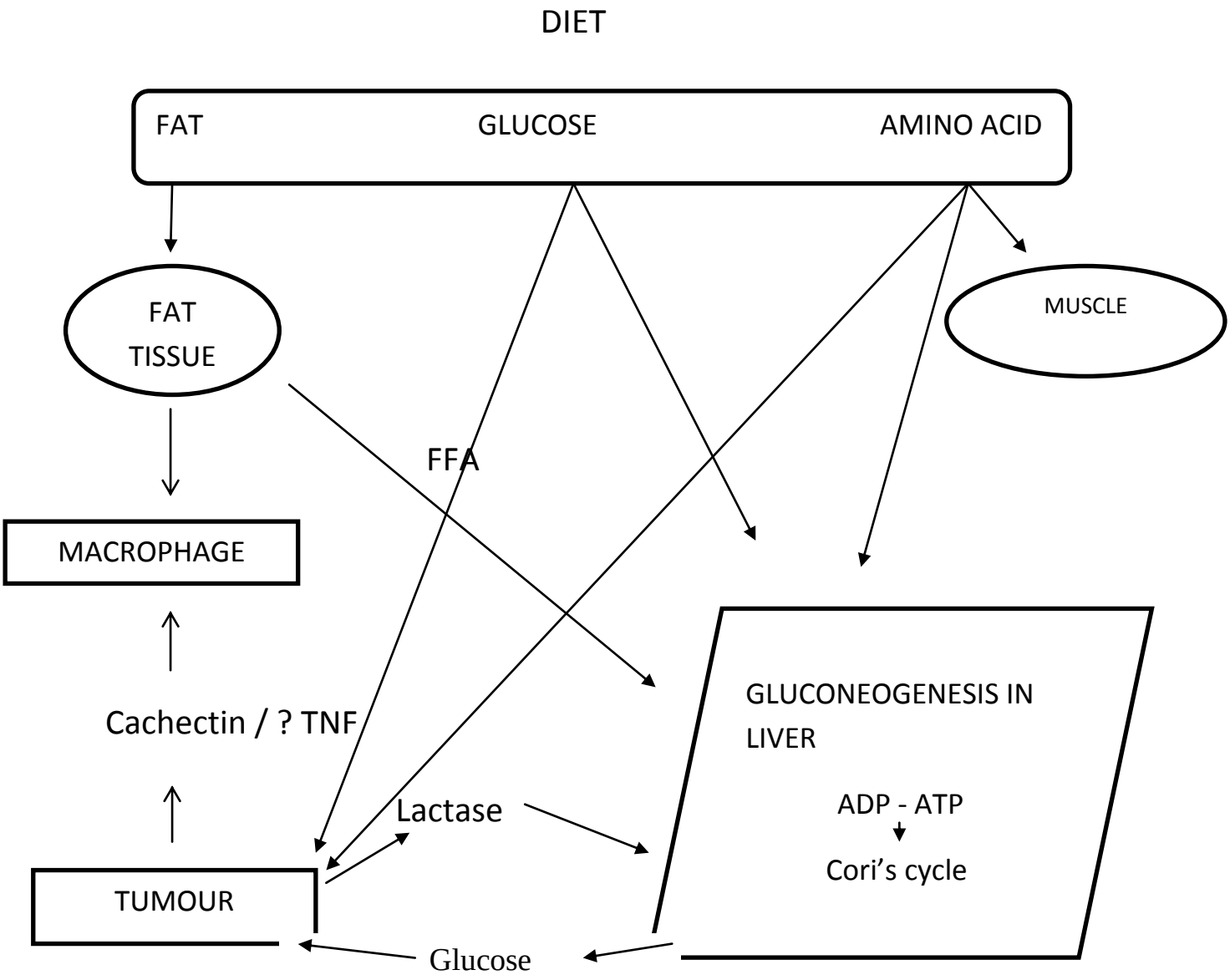
Both under or overweight has potential epigenetic influence and nutritional insufficiencies can lead to up-regulation or down-regulation of various genes[13]

Mechanism of under nutrition

Children with cancer experience lot of energy imbalance[8]. There are changes involved in carbohydrate, fat and protein metabolism leading to malnourishment.

Changes in the metabolism of fat, glucose and amino acids (AA) induced by the presence of the tumour is shown below:

There is increased lipid breakdown and increased protein turn over resulting in weight loss. These children have high caloric expenditure. They utilise both dietary glucose and glucose from gluconeogenesis and from amino acids. Glucose is converted to lactate which is recycled by liver with lot of energy expenditure. Release of Cachectin and TNF leads to decrease in total body fat..



FFA – Free fatty acid TNF – Tumour necrosis factor

There is also the other end of the spectrum –overweight and obesity. Obesity at diagnosis is associated with high risk of obesity at the end of treatment and survivorship.

Effect of under nutrition on treatment outcome

Mendizabal et al[1] showed that children who presented with malnutrition at diagnosis had significantly worst outcome than well-nourished children in terms of disease free survival and relapse. Forty three paediatric patients with standard risk ALL were studied. Of the 43 patients 37% presented with malnutrition at diagnosis. The 5 year disease free survival (DFS) was 83% in well-nourished and 26% in undernourished children ($p < 0.001$). Relapses were more frequent in bone marrow in undernourished group than the well- nourished group, 56% Vs 7% ($p< 0.0001$).

Begum et al[2] compared the outcome of undernourished children versus well-nourished children with regard to induction of remission. This prospective study included 60 children with ALL, between 1-15 years of age. Groups were divided based on weight for age. Thirty children were undernourished and thirty were well-nourished. It was found that the number of days required to achieve remission in the under nourished children were longer (39±0.72 days Vs 31.63±0.17 days) and statistically significant ($p < 0.04$).

A multivariate analysis by Viana et al[3] looked at the influence of nutritional status with the probability of overall survival and duration of first complete remission in 128 children treated for ALL. It was found that weight for age z score of < -2 was a poor prognostic factor.

Roy et al[4] did a retrospective analysis in 159 children with ALL, to assess the influence of malnutrition on treatment tolerance, treatment related complications and treatment outcomes during induction and maintenance. Haematological toxicity was more in severely malnourished children.

Remission rates were less and relapse rates were proportionately more in malnourished children. Thirty children were severely malnourished. The incidence of febrile neutropenia was significantly higher in severely malnourished children than well- nourished children (Mean 3.8vs1.42, p< 0.001).

Hafiz MG et al[5] Conducted a prospective study to evaluate the nutritional status at initial presentation and to correlate the effects of nutrition on induction of remission. This was conducted in Dhaka, Bangladesh during period of 1 year from July 2006 to June 2007.66 children were diagnosed between period of 1 year from 1-15 years irrespective of sex. Thirty five (53.03%) children were under- nourished and thirty one (46.97%) were well nourished. The under nourished children during induction had culture proven/clinically documented infections 2-3 times more frequently than well nourished children. They also required longer duration of induction (p<0.001) and prolonged period of hospital stay (p<0.001).

Mejia-Arangure et al[14] conducted a prospective study in children with ALL. They included 163 patients below 16 years of age. Nutritional groups were made based on weight/height (waterlow's classification). In the malnourished group 46% completed treatment and were alive, 9.8% had relapse, 45% died whereas in the well -nourished group 59% completed treatment and were alive, 21.3% relapsed and 19% died. The risk of death during initial phase of treatment was 2.6 times higher in the malnourished group than the well -nourished group despite lower relapse rate. The risk of death increased with increasing severity of malnutrition.

Previous studies have shown the influence of weight at the time of diagnosis on event-free survival (EFS) and treatment related toxicity (TRT) in childhood ALL. More recently Orgel et al[15] from the Children's Oncology Group correlated outcomes to the duration of weight extremes during treatment for paediatric acute lymphoblastic leukaemia (ALL). The authors evaluated the prognostic implications of weight extremes during intensive phase of therapy for ALL. A total of 2,008 children who were treated for high risk ALL in the

Children's Oncology Group study CCG-1961, were included in the study. The effect on EFS and TRT (treatment related complication) of extreme weight (either obese or underweight) at diagnosis and cumulative time with an extreme weight between end of induction and start of maintenance therapy was analysed. Obese and underweight patients had 5 year EFS rate of 64%±3% and 65%±5%,respectively,as compared with 74%±1% for normal/overweight patients (univariable P = 0.002)

Analysis of EFS was done from the start of maintenance for 1,581 patients alive and disease free at that time. There were 644 patients (40.7%) who had extreme weight (393 obese and 251 underweight), whereas 937 patients (59.3%) were normal/overweight during their treatment. Children who were either obese or underweight had inferior EFS as compared with those who did not have extreme weight (univariable *P*=0.008). If children were obese or underweight for >50% of their treatment time, EFS was 73%±3% and 70%±5% respectively. The EFS for children who were obese or underweight for < 50% of the time during treatment was 77% ± 3% and 82% ±3%, respectively.

This study showed that patients who presented obese or underweight and remained so for ≥ 50% of the pre maintenance phases ((≥ 50% obese: HR, 1.43; 95% CI, 1.04 to 1.96 and ≥ 50% underweight (HR, 2.30; 95% CI, 1.46 to 3.63; global *P* < .001) had the greatest risk of an event. In contrast children who presented obese or underweight but normalised their weight for > half of pre maintenance therapy had similar risk in comparison to children who were never obese or underweight. There was a protective effect noticed for those who started in the normal weight category at diagnosis but became underweight for < half the pre maintenance period (HR, 0.52; 95% CI, 0.32 to 0.83).When further analysed, BMI at diagnosis and BMI as a continuous linear-quadratic element, the cumulative time–spent effect

remained significant at $P \leq .004$, which shows that the effect was not attributable to differences in the distribution of weights at presentation.

There was statistically significant association between weight category and risk of grade 3 and 4 toxicity (higher rates of TRT at both extremes of weight*;* P =0.008) during 13946 courses of treatment among 2008 high risk patient cohort. There was also a risk profile of toxicity which was specific to weight category. Hepatic and pancreatic toxicities were more common among obese patients both P <0.001. In contrast, pulmonary toxicity and fungal infections were more common among P =0 .001

Underweight children also had more severe hematologic toxicity, as evidenced by the use of more hematologic support P <0 .001, including blood product transfusion and the use of hematopoietic growth factors.

Effect of obesity/ overweight on treatment outcome

There are very few studies that looked at the treatment outcome in children with obesity at the time of diagnosis. In a recent study by Aldhafiri et al[16]> 40% of all patients were underweight, overweight or obese at diagnosis. A retrospective analysis was done by Butturini et al[6] in 4260 ALL children enrolled between 1988-1995.Three hundred and forty three (8%) children were obese. The 5 year EFS (event free survival) in obese Vs non obese children was 72±2 Vs 77±0.6(p 0.02).The relapse rate was also higher in the obese group 26±2.4Vs 20±0.6(p 0.02). But this association was not seen in patient younger than 10 years. The poor outcome in both univariate and multivariate analysis in obese children was significant for children > 10 years of age at diagnosis.

Nutritional status following completion of treatment

Childhood leukaemia survivors are at risk for several possible late effects of the disease or treatment. Obesity can be considered one of the most important health conditions in patients treated for childhood cancer, especially in ALL survivors. In paediatric ALL, the rate of obesity ranges between 40-50% from the end of treatment to 5 year post treatment.[17-20] · Hence, survivors of ALL are prone to develop metabolic co-morbidities like dyslipidaemia, insulin resistance and hypertension. It is also found that overweight patients when diagnosed to have leukaemia after 10 years of age had low mean 5 year EFS(event free survival) and increased risk of relapse than normal weight patients[6].

There are many studies which have analysed the long-term prevalence of obesity in childhood after the end of ALL treatment. Table below shows various studies where children have been followed up from minimum of 4 years till adulthood after completion of ALL treatment. The rate of obesity ranges between 40-50% from the end of treatment to 5 year post treatment. Odame et al[21] followed children for 4 years after treatment and found that the prevalence of obesity was more in girls (57%) than in boys(21%). Jarfelt et al[27] followed up patients for a minimum of 15 years and reported a prevalence of 34%.

AUTHOR	NUMBER OF PATIENTS	ASSESSMENT TIME	PREVALENCE OF OBESITY (%)
Odame et al [21]	40	Diagnosis +4 years	57 girls 21 boys
Van Dongen Melman et al[22]	113	Diagnosis +4 years	24
Talvensaari et al[23]	50	Diagnosis +13 years	32(vs 10 in controls)
Reilly et al[24]	98	Diagnosis +3 years	16
Nysom et al[25]	95	Diagnosis +11 years	25
Meacham et al[26]	1665	Adulthood	18 girls 16.5 boys
Jarfelt et al[27]	35	20(minimum 15 yrs)	34

Mechanism of obesity in children in the post treatment period

Being overweight/obese at the time of diagnosis and excessive weight gain during treatment were significant predictors of being overweight/obese after treatment. Weight at diagnosis has an influence on the weight gain during and at the end of treatment[28]. Excessive weight gain during treatment is unlikely to be reversed after completion of treatment.

There are various factors implicated in increase weight gain after successful treatment for ALL

- Cranial irradiation
- Specific chemo related complications
- Steroid use
- Growth hormone deficiency
- Role of leptin
- Theory of premature adiposity rebound(AR)
- Lifestyle changes

Cranial radiation increases the risk of obesity in survivors[29]

Craig et al[30] reported the effect of radiation on CNS and its association with gender and dose of radiation during treatment. The study determined the effect on BMI Z score at final height of age at diagnosis, sex and the radiation dose that was given. Patients were divided based on the sex and radiation dose, 18-20 Gy and 22-24 Gy. There was increase in BMI Z score at final height for female children who received a dose of 18-20 Gy. Recent study by Khan RB et al[31] have shown that upto 83% of long term survivors of ALL have increased neurological morbidity and decreased quality of life.

Drugs

Vaisman et al[32] showed the effect of specific chemotherapy agents like Methotrexate and Mercaptopurine to have an effect on metabolic fuel use and protein synthesis and turnover.

Mechanisms of development of metabolic syndrome due to various chemotherapy agents are listed below. Other than these, Actinomycin, Bleomycin and platinum drugs used for treatment of other tumours also contribute to obesity in children.

Drugs	Metabolic effect
Alkylators	Obesity, Dyslipidaemia, Steatosis, Insulin resistance, Hypertension, Impaired glucose flux into liver.
Anthracyclins	Obesity, Dyslipidaemia, Steatosis, Insulin resistance, Hypertension, Metabolic endo-toxemia.
Anti-metabolites	Adiposity, Atherosclerosis, Steatosis, Insulin resistance, Impaired glucose flux into liver, Metabolic endo-toxemia
Vinca Alkaloids	Hypertension, Hyperglycaemia, Altered liver glucose Metabolism, Steatohepatitis, Increased calorie absorption.

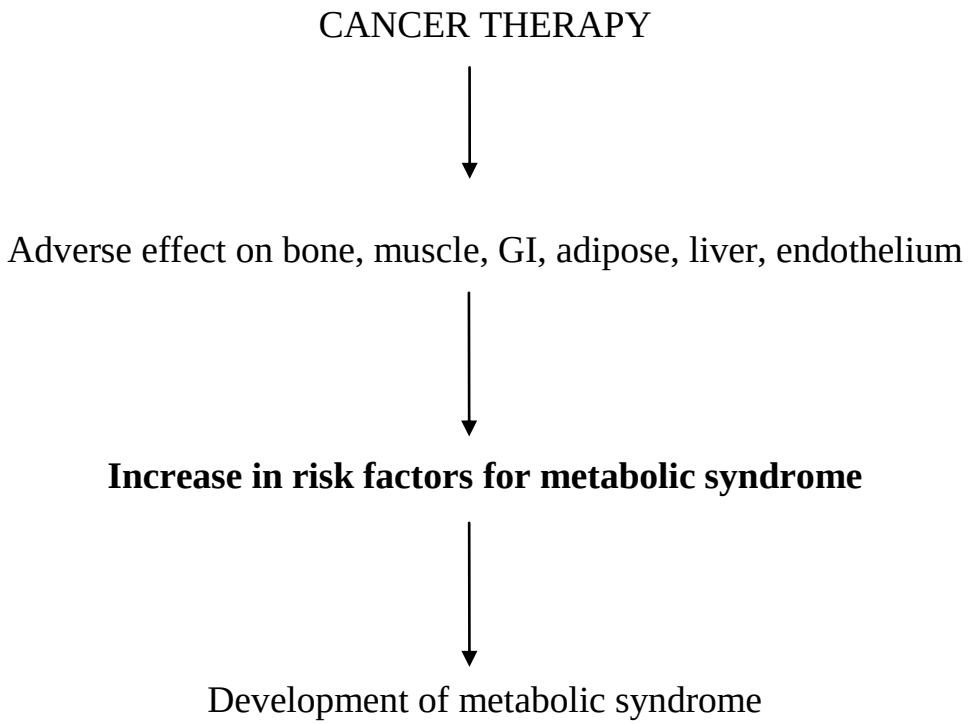
Corticosteroids

Corticosteroids are well known for their effect on weight gain. They lead to obesity by various mechanisms- effect on appetite, regulation of energy intake, alteration in substrate oxidation, alterations in energy expenditure, increased adiposity due to suppression of growth hormone and resistance to leptin.

The end organ effect of chemotherapeutic agents and steroids and its mechanism in metabolic syndrome have been extensively given by Rosen et al[29]

Many tissues involved in lipid metabolism and glucose homeostasis are affected by chemotherapy.

Treatment for ALL has adverse effect on various tissues/organs which leads to increase in risk factors of metabolic syndrome like obesity, insulin resistance, dyslipidaemia, atherosclerosis and hypertension. This in-turn is responsible for the outcomes like Type 2 diabetes, cardiovascular disease etc.



Bones:

Bones play an essential role in metabolic health. Osteocalcin is an osteoblast specific protein that promotes beta cell proliferation and insulin secretion-this improves insulin sensitivity. This protein is low in children undergoing cancer chemotherapy. Low osteocalcin is predictive of insulin resistance. Both chemotherapy and radiotherapy leads to depletion of osteogenic precursors and osteoblasts.It also has adverse effect on osteoblast activity. High dose of steroids cause bone loss which is persistent and osteonecrosis. Avascular necrosis is a major adverse effect of steroids on the bone.

Muscle:

Steroids impair the synthesis and breakdown of muscle protein. Drugs like Vinca Alkaloids disrupt the functional integrity of microtubules. Survivors are unable to maintain body composition as there reduced muscle mass, decreased sarcolemma surface area and decreased resting thermogenesis. Muscle mass is reduced by various mechanism like decreased physical activity during treatment and motor neuropathies. Decreased sarcolemma surface can lead to overt type 2 diabetes by decreasing whole body insulin-stimulated glucose uptake. As the microtubules are destroyed there is decreased glucose uptake and transport by skeletal muscles due to GLUT 4 vesicle translocation. This pathology in the skeletal muscle predisposes to atherogenic dyslipidaemia.

GIT:

Certain chemotherapy agents decrease gut motility and affects the constitution of microbiota. Before development of obesity, there is change in the composition of the gut microbiota. Use of broad spectrum antibiotics leads to changes in the gut flora. This leads to modification of the gut flora. Physical disruption of the gut barrier leads to leakage of lipopolysaccharides (LPS) into the blood. This acts as a trigger for the development of metabolic endotoxemia which is in turn a risk factor for atherogenesis and insulin resistance.

Liver:

Alkylators, anti-metabolite etc are known to cause SOS- Sinusoidal obstruction syndrome. Glycogenesis, lipogenesis, fatty acid oxidation, mitochondrial oxidation and oxidative phosphorylation are affected. When cells cannot oxidise fatty acid ,they are exported leading to dyslipidaemia. Survivors are also prone for focal nodular hyperplasia.[33]

Adipose tissue:

Adiponectin which regulates lipid and glucose metabolism id reduced is decreased leading to endothelial damage and atherosclerosis.

Endothelium:

Chemotherapy affects endothelial function by disrupting the nitric oxide (NO) pathway. Certain drugs causes increase in production of oxygen free radicals leading to oxidative stress. This uncouples endothelial nitric oxide synthase, resulting in production of superoxide anion rather than vasodilator (NO). This causes arterial stiffness and hypertension in childhood cancer survivors. Endothelial function assessed by flow-mediated dilation has been shown to be associated with development of diabetes.

Role of leptin in obesity

Mechanism that explains the relation between cranial radiation therapy and obesity is leptin insensitivity.[35] Leptin[34,36] is a hormone derived from the adipocytes .It binds to the biologically active form of its receptor (LEPR) in the hypothalamus. Radiation-induced damage of this axis could possibly disrupt the leptin signal and lead to obesity. As very few survivors developed this complication leptin receptor polymorphism[35] particularly to LEPR GlnQ223Arg was suspected as cause of obesity in female survivors.

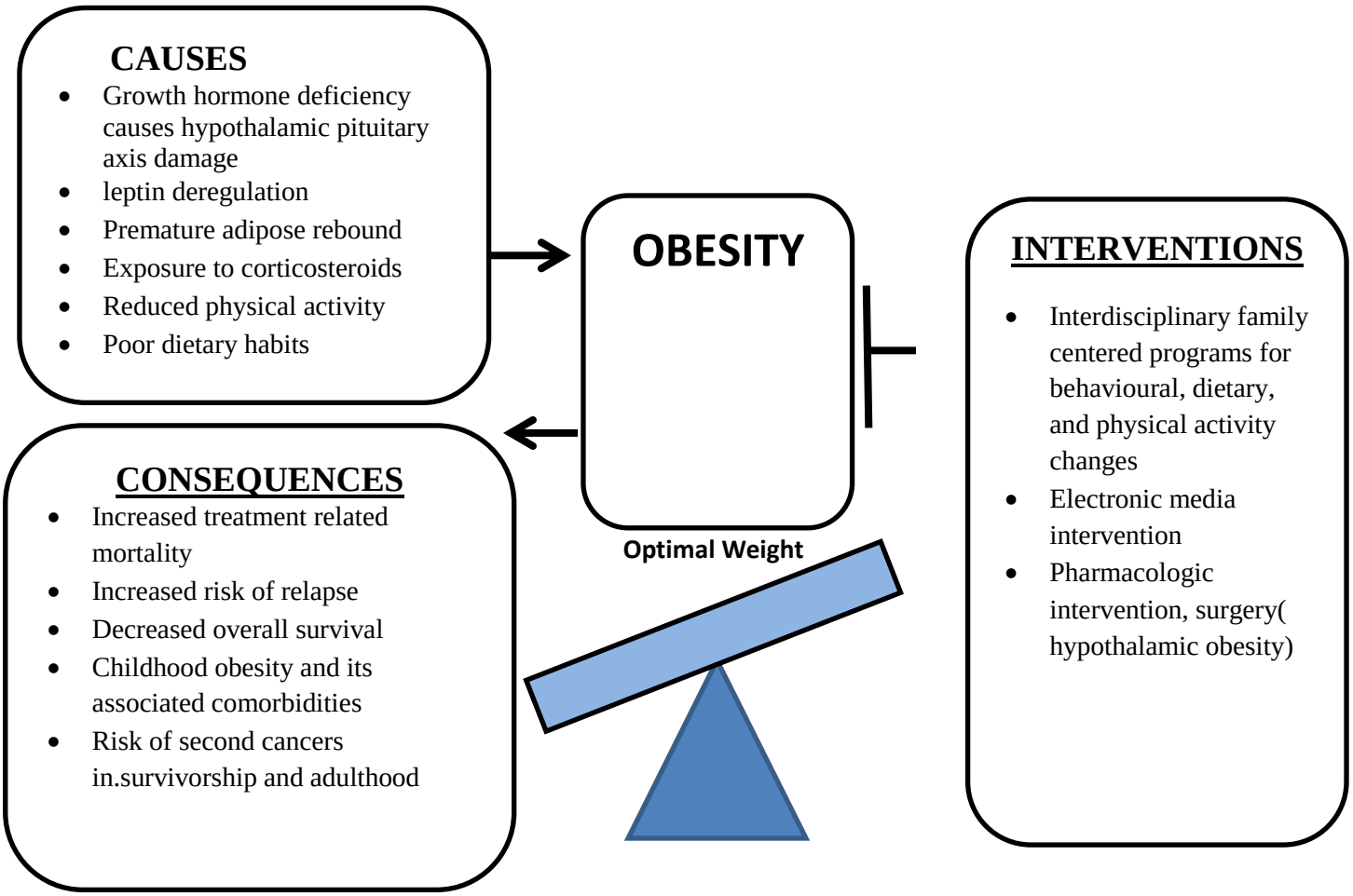
Adiposity rebound in obesity

Adiposity rebound (AR)[37] -"is the point at which BMI increases after its nadir in childhood". The nadir of AR coincides with peak occurrence of ALL. Hence AR is a crucial period in the development of obesity. Younger age of onset of AR is an increased risk of high BMI and development of obesity.

Life style changes

During chemotherapy there is a major change in the lifestyle of the patient. Loss /decreased physical[20,28] activity occurs during hospitalization. Factors taken into account for decreased physical activity includes diminished interest, over protectiveness of the care takers, steroid related myopathy and Vincristine related neuropathy. It has been found that even after treatment there is reduced physical activity in survivors of malignancy than the normal healthy siblings.

Major causes and consequences of obesity in childhood cancer patients and /or survivors with recommended interventions[34] are given as follows



Obesity /overweight in children completed treatment of ALL

Zhang et al[38] evaluated the longitudinal changes in the rate of obesity and BMI z –scores in ALL children during and after their treatment for cancer. This was a retrospective study which involved paediatric ALL patients treated between 1985-2010 at Floating Hospital for Children at Tuft's Medical Centre. It included patients < 21 years with Pre-B ALL (Standard or high risk) or T-cell ALL (high risk).There were 83 patients finally included in the study. The longitudinal weight changes showed that 20.5% were overweight and 10.8% obese at diagnosis, by the end of induction 41% were overweight/obese. However there was a decrease at end of consolidation where 25.3% were overweight/obese. There was an increase in BMI again at during the first 6 months of maintenance (39.7%).The number of children who were overweight/obese at the end of treatment and 5 year post follow up was 38.2% and 40.5% respectively. Of these, 81.3% remained overweight/obese at the end of treatment and 66.7% remained overweight /obese 5 years post treatment. This shows that children with ALL are at increased risk of becoming overweight /obese early in treatment. Increases in weight are maintained throughout and after treatment. This study clearly shows that high BMI z- score at diagnosis was associated with an increased risk of being overweight /obese at treatment completion (odds ratio=2.9,95% CI:1.6-5.1).Weight gain during treatment was associated with being overweight /obese 5 years post treatment (odds ratio=3.8, 95% CI: 1.1-12.5). Thus this study shows that the status of weight /BMI z-score at the time of diagnosis is a significant predictor of being overweight/obese at the end of treatment. This emphasises that intervention should be undertaken to control weight during early treatment –especially for children who are overweight /obese at the start of treatment.

Obesity and hypertension are well known in survivors of ALL. Elevated parental BMI was associated with elevated BMI at diagnosis. A study by Esbenshade et al[39] in 183 patients with paediatric ALL diagnosed during 2000-2008 analysed the changes in BMI and blood pressure over the course of treatment of ALL. This was a retrospective cohort ranging from 1-21 years at diagnosis .These children were diagnosed as standard or high risk Pre-B ALL/T- cell ALL .The Children's Oncology Group (COG) protocol was followed. The BMI z- score showed an increase ($P<0.001$) from induction to consolidation then decreased ($P < 0.001$)at the start of delayed intensification. BMI was again found to increase during early part of maintenance. Blood pressure analysed showed that 31.1% had systolic pre-hypertension and 18.6% had diastolic pre-hypertension during the course of therapy.41.5% had systolic hypertension and 24% had diastolic hypertension.

Study by Withycombe et al [10] in 1638 patients between 1996-2002 also found that treatment of high risk childhood ALL was associated with excess weight gain from the beginning of maintenance through the end of treatment. By the end of treatment 23% were obese, compared with 14% at diagnosis. Mean BMI % remained high throughout treatment for those who were obese at diagnosis. Thus high prevalence of obesity poses a challenge for paediatric oncologist. It has to be approached and addressed effectively through multidisciplinary approach. There is a need to assess changes in BMI at several points from diagnosis until several years after completion of treatment.

Central obesity has a very important implication regarding health as it is an adverse effect in children. Hence methods to measure central obesity is needed for early intervention. Waist circumference is an alternative to the measurement of BMI in terms of defining adiposity. Waist circumference (WC) is measured with a non-stretchable tape by trained nutritionists (exerting the same standard pressure on the tape) at the midpoint of the lowest rib cage and the iliac crest, to the nearest 0.1 cm in a standing position during end-tidal expiration.

Taylor et al[40] compared WC, waist hip ratio(WHR) and conicity index to see which one was significantly better to determine trunk fat mass. This study has demonstrated that WC is a simple method that can be used for screening high central adiposity.

Study by Kurian R et al[41] provides reference values and percentile curves for waist circumference and Wt /Ht ratio of urban Indian children. It has been suggested that the 75th percentile of waist circumference from the study can be used as an "action point" for Indian children to identify obesity and help in early intervention.

Waist circumference has been very well correlated with other metabolic syndrome parameters like blood pressure, lipid profile , fasting blood glucose and fasting insulin levels in normal children. Zhang YX et al[42] has shown the prevalence of high blood pressure with high WC percentile among normal children and adolescents. This study showed included 6895 children(3453 girls and 3442 boys)- whose age ranged between 7-17 years. There was increase of 5.4 times and 2.4 times (in boys and girls respectively)in blood pressure when the WC was > 95^{th} centile.

A cross sectional study[43] was done on 188 healthy obese children between 7-11 years to determine where routine assessment of waist circumference has predictive value for developing cardiovascular risk factors and diabetes mellitus. $\geq 90^{th}$ centile was taken as high waist circumference .Children with high WC had low High density cholesterol (HDL), high Triglycerides(TG) and increased fasting glucose level, indicating that high waist circumference correlates with high risk of insulin resistance and dyslipidaemia.

Summary

Review of literature has clearly illustrated the importance of nutritional status assessment, mechanisms of both under and over nutrition and its effect on overall health of cancer survivors. Both underweight and overweight in children with cancer is not desirable. Optimum nutritional status is required to cope with the demands of the disease and its long term treatment effects. Nutrition thus becomes one of the fundamental parts of care of children with cancer and should be recognised as crucial step in cancer treatment. Appropriate and adequate nutrition is needed to maintain optimal growth and development. This will in-turn enhance the survival out-come, decrease the toxicity and improve the quality of life in these children.

Based on this information, we carried out this study on longitudinal assessment of nutritional status of children with ALL and its effect on outcome and quality of life.

MATERIALS AND METHODS

MATERIALS AND METHODS

Data retrieval

Data from medical records of 241 children with ALL was retrieved during the study period. Patient's demography, risk stratification, treatment received, complications, outcome and follow up visit information were collected by the investigator. Weight and height were available for children at diagnosis, during treatment - at the beginning of delayed intensification and maintenance phase as well as at end of treatment. Following completion of treatment children are followed up once in 3 months in the first year , twice in the second year and annually thereafter till the 5^{th} year.

Inclusion criteria: Children completed treatment for ALL by July 2014

Exclusion criteria: Children not yet completed maintenance phase of treatment

Risk stratification of children with ALL was used based on international guidelines, with minor modifications.

Factors	Standard risk	Intermediate risk	High risk
Age in years	>1,<10	<1,>10	
WBC/cumm	<20,000	>20,000	>1,00,000
IPT	Pre B ALL	T cell ALL	T/Pro B ALL
Cytogenetics	t(12;21)	t(1;19)	t(9;22),t(4;11)
CSF	Negative	positive	
Testes	Negative	positive	
Prednisolone response	PGR	PGR	PPR
BMA	M1	M2	M3

PGR- Prednisolone good response-day 8 peripheral blood absolute blast count should be < 1000.

PPR- Prednisolone poor response

Bone marrow aspirate (BMA) M1 blasts < 5%

M2 blast 6-25%

M3 > 25% blast

Treatment

Once they are stratified, treatment is instituted based on their risk group. Outline of treatment is shown here. Details are available in Annexure no 1.

TREATMENT

Pre- induction

↓

Induction

↓

Consolidation

↓

Interim Maintenance

↓

Delayed intensification

↓

Maintenance

Assessment of nutritional status of children

Using weight and height, BMI was calculated for children older than 2 years of age at diagnosis and they were divided into under nourished, well-nourished or overweight/obese. Outcome parameters such as response to treatment, number of febrile episodes, overall survival and event free survival were compared between these groups.

Height was measured to the nearest millimetre with a wall mounted Harpenden Stadiometer.

Weight was measured with electronic scales to the nearest 0.1 kg. BMI (kg/m2) was calculated.

Waist circumference was measured (cm) in duplicate with an anthropometric tape while the subjects were wearing light clothes.

Body Mass Index(BMI) = Weight(kg) / Height(m)^2 .BMI centiles were calculated using the US Centre for Disease Control and Prevention program for children between 2 and 20 years of age (http://www.cdc.gov/growth charts)

Children's nutritional status classified based on BMI using CDC growth charts is as follows

Undernourished children	< 5th centile
Well-nourished children	5-85th centile
Overweight children	> 85th centile but < 95th centile
Obese children	≥ 95th centile

Screening for metabolic syndrome: Overweight /obese children were evaluated further for early signs of metabolic syndrome by measuring waist circumference, lipid levels, HbA1C, blood insulin and sugar levels. Tanner's staging was also looked at. Parents' weight and height were also measured and their BMI was calculated. This data was compared with children's nutritional status.

Glucose insulin ratio (GIR) It is the ratio of fasting glucose level and fasting insulin level.

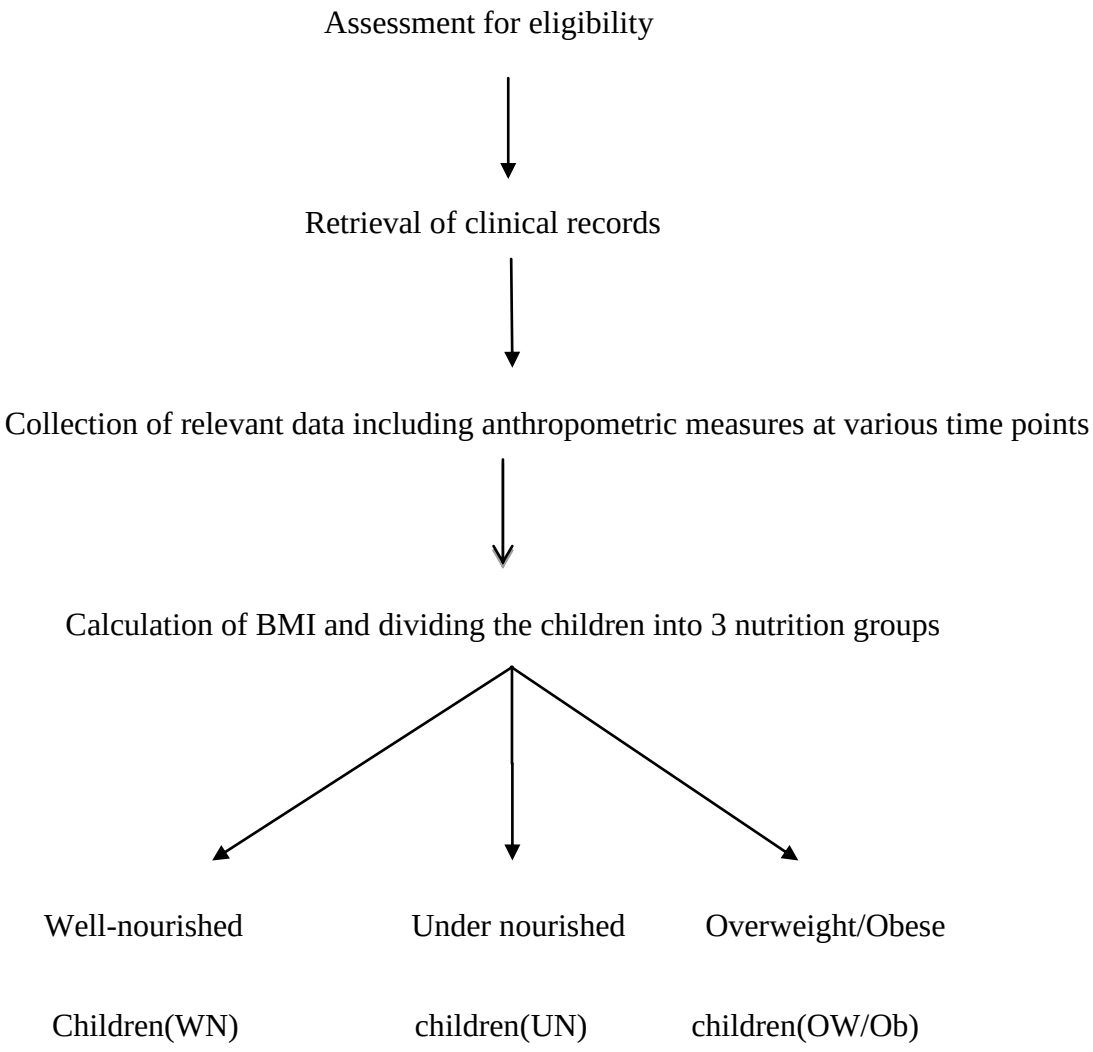
DEFINITION OF THE OUTCOME VARIABLES IS AS FOLLOWS:

1. Early response to treatment: The early response to treatment is based on day 8 blast count after 7 days of prednisolone 60 mg/m^2/day with or without intrathecal Methotrexate. The response to treatment is good prednisolone response if absolute blast count is < 1000/cu.mm.

2. Induction remission: The child is in remission if day 35 bone marrow during end of induction phase shows < 5% blast with Absolute neutrophil count (ANC) > 1000/cu.mm and platelet count > 1 lakh/cu.mm without any evidence of extra medullary disease.

3. Febrile neutropenia: Fever is defined as single oral temperature > or = 38.3 C (101F) single reading or > 38 C (100.4F) sustained over 1 hour. Neutropenia is defined as ANC < 500 cells/cu.mm or < 1000/cu.mm with expected fall below 500/cu.mm over the next 48 hours. We only included high febrile neutropenia requiring admission.

ALGORITHM:


Assessment for eligibility
Retrieval of clinical records
Collection of relevant data including anthropometric measures at various time points
Calculation of BMI and dividing the children into 3 nutrition groups
Well-nourished Children(WN)
Under nourished children(UN)
Overweight/Obese children(OW/Ob)
And assessment of the effect of nutritional status on various outcomes

Screening for metabolic syndrome in children who completed treatment

Assessment of eligibility

↓

Informed consent in overweight and obese children

↓

Measurement of waist circumference, blood pressure, and tanner's staging was done. Blood samples for lipid levels, fasting glucose, insulin levels and HbA1c was collected. The presence of hypertension, hyperlipidaemia and impaired glucose tolerance was looked at.

Statistical Methods

Descriptive statistics for continuous variables was derived with mean and standard deviation or median with IQR (interquartile range) and frequencies with percentages for categorical variables. Chi-square test and Fischer's test was used to compare proportions. The effect of various factors including nutrition on the outcome variables was analysed using Cox regression analysis.

Sample Size Calculation

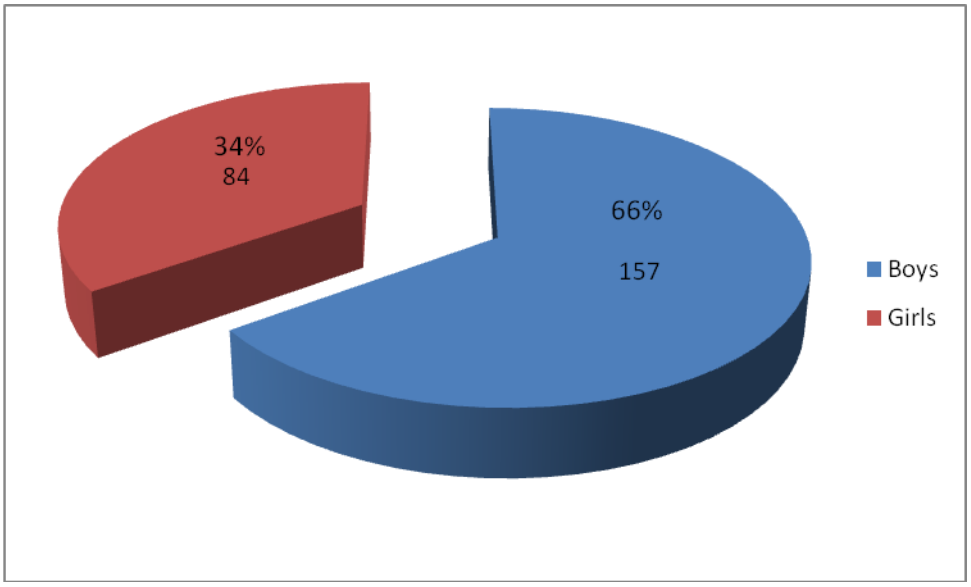
A sample of size of 226(113 in well-nourished and 113 in the moderately & severely malnourished) children will be required to detect a 15 % difference in achieving remission between the 2 groups at 80% power and 5% level of significance. We assume that the remission rate is 90 % in well-nourished group and 75% in moderately and severely malnourished group after completion of induction phase.

RESULTS

RESULTS

Two hundred and forty one children treated for Acute Lymphoblastic Leukaemia (ALL) were included in this analysis.

Figure 1: Male: Female ratio of the study population



There were 157 boys and 84 girls. The male: female ratio in this group was 7:3

Age at diagnosis

The age at diagnosis of these children ranged from 11 months to 15 years; the mean age at diagnosis was 5.9 years (11months- 15 years). Children were divided into four groups based on their age; <1 year, 1-5 years, 6-10 years and >10years.

55% of our study population were less than 5 years old at the time of diagnosis.

Table-1 Age at diagnosis

N = 241

Age	No. of Children	Percentage(%)
<1yr	2	1
1-5 yrs.	130	54
6-10 yrs.	78	32
11-15 yrs	31	13
Total	241	100

Figure 2: Age at diagnosis

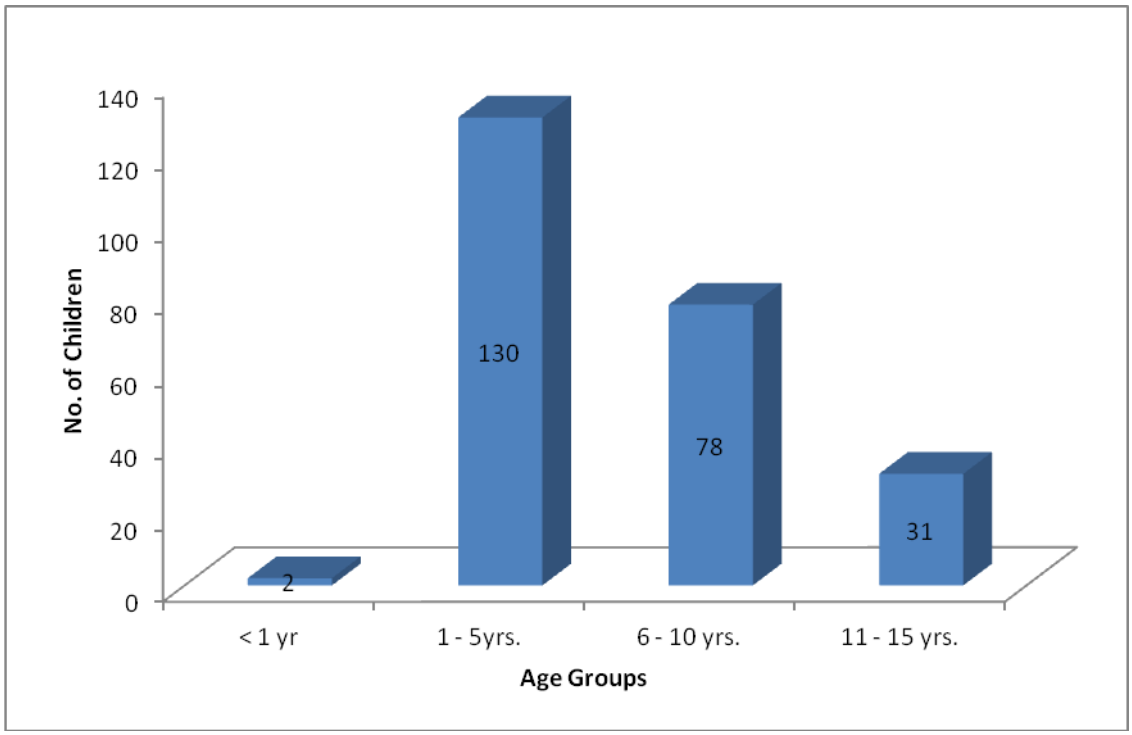


Table 2: Age and gender distribution at diagnosis

N = 241

This table and graph show age and gender distribution of the study population. In all age groups the ratio of boy's: girl's was approximately 2:1.

Age	Boys	Girls
<1yr	2	0
1-5 yrs.	83	47
6-10 yrs.	51	27
11-15 yrs	21	10
Total	157	84

Figure 3: Age & Gender of the children at diagnosis

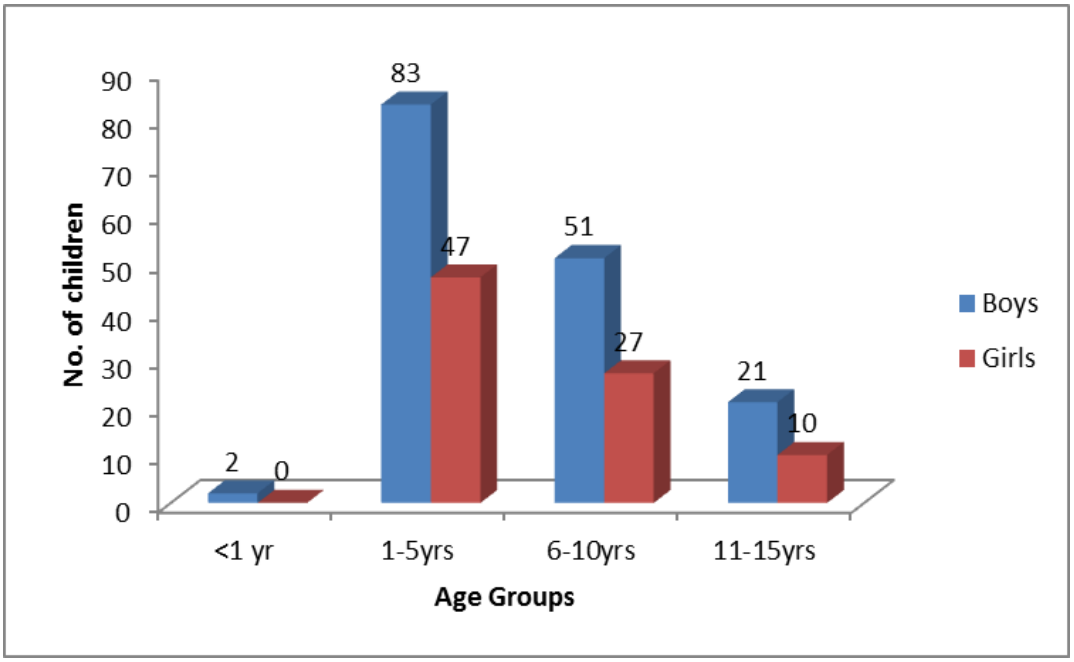


Table 3: Type of ALL

N=241

Most common type of ALL in this population was Pre B; followed by T cell ALL.

Bi-phenotype and Pro B constituted only < 5% .

Type of ALL	No. of children	Percentage (%)
Pre B	194	81
T cell	34	14
Bi-phenotypic	8	3
Pro B	5	2
Total	241	100

Figure 4 :Type of ALL

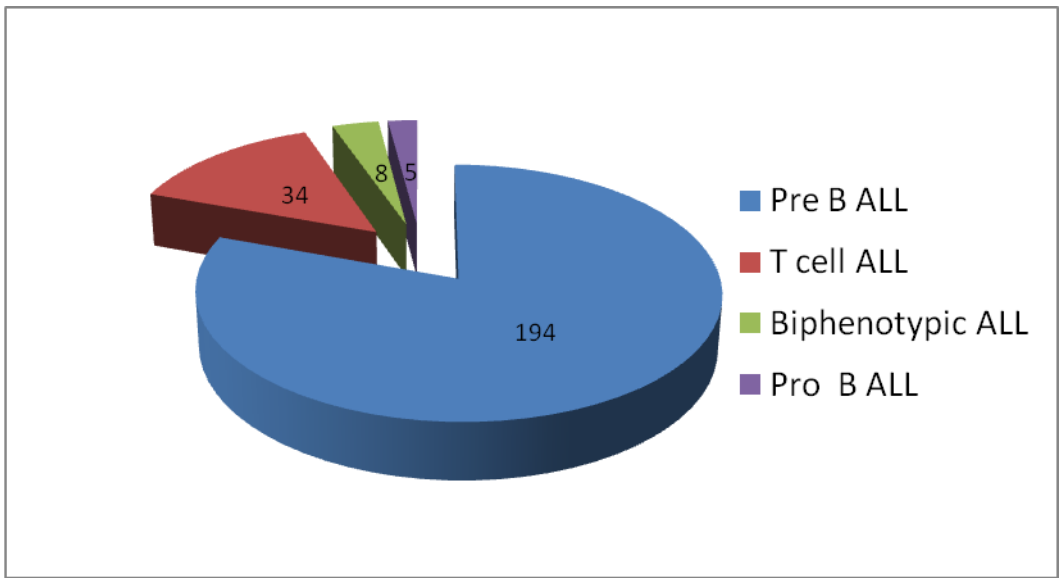


Table 4: Type of ALL vs Gender (N= 241)

Type of ALL	Boys	Girls	Total
Pre B	122(63%)	72(37%)	194
T cell	26(75%)	8(25%)	34
Bi-phenotypic	6(75%)	2(25%)	8
Pro B	3(60%)	2(40%)	5
Total	157	84	241

In this table and graph, we looked at type ALL and male: female ratio. In all groups 60-75% were boys.

Figure 5 : Type of ALL vs Gender

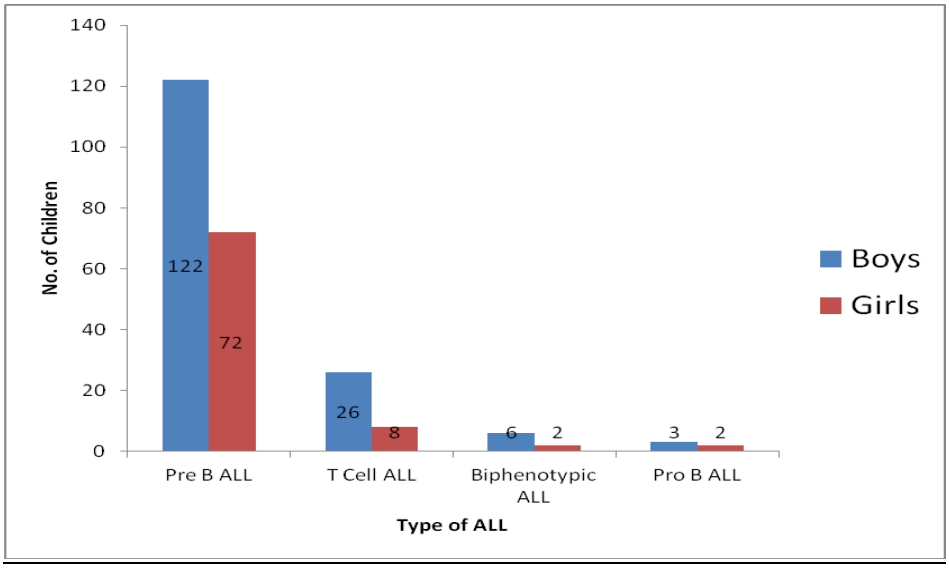


Table 5: Type of ALL vs Age

N = 241

Age	Pre B	T cell ALL	Bi-phenotypic	Pro B	Total
<1yr	1(50%)	0	0	1(50%)	2
1-5 yrs.	111(86%)	9(7%)	7(5%)	3(2%)	130
6-10 yrs.	57(73%)	20(26%)	0	1(1%)	78
11-15 yrs	25(81%)	5(16%)	1(3%)	0	31
Total	194	34	8	5	241

In all age groups, except <1year, Pre B ALL was the predominant type of leukaemia.

Table 6: WBC count vs type of ALL

	WBC <20,000	20,000 – 1,00,000	>100,000	Total
Pre B	11	165	15	191
T cell	0	16	21	37
Bi-phenotypic	2	6	0	8
Pro B	1	2	2	/5
Total	14(6%)	189(78%)	38(16%)	241

When children were divided based on the WBC count at diagnosis, majority (78%) had counts ranging from 20-100 thousand. 6% had <20,000/c.mm and 16% had >1Lakh WBC at diagnosis.

11/14 (78%) children with WBC<20,000 had Pre B ALL. None of the T ALL had low WBC count at presentation.. Among those with high WBC at diagnosis, 55% had T ALL.

Among all cases of T ALL, 57% had >100,000 WBC at diagnosis

CNS and Testicular Disease:

All children had a diagnostic lumbar puncture done at first admission. Those who had >5 blasts in the CSF or any parenchymal disease or cranial nerve palsies were considered to have CNS involvement. Children with enlarged testes at diagnosis were diagnosed to have testicular disease.

38/241 (16%) had CNS disease and 3/157(2%) boys had testicular disease in our study population.

Table 7: CNS disease vs Gender

N = 241.

Gender	CNS disease Present	CNS disease Absent	Total
Boys	27 (17%)	130 (83%)	157
Girls	11 (13%)	73 (87%)	84
Total	38	203	241

P = 0.09

17% of boys and 13% of girls had CNS disease. There was no significant difference in the incidence of CNS disease between boys and girls.

Figure 6: CNS Disease vs Gender

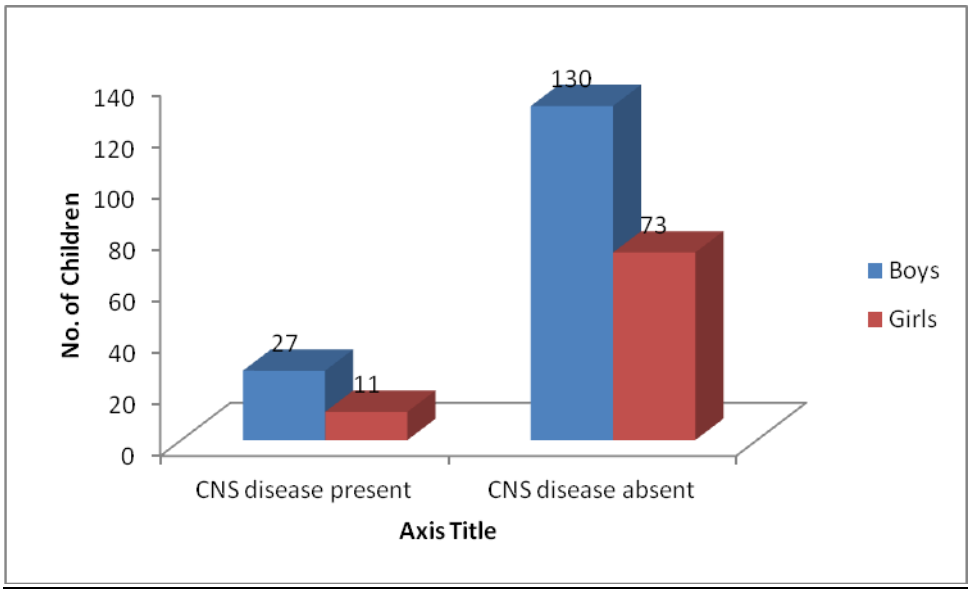


Table 8: CNS disease vs type of ALL

N =241

Type of ALL	CNS disease Present	CNS disease absent	Total
Pre B	24(12%)	170	194
T cell	9(26%)	25	34
Bi-phenotypic	3(38%)	5	8
Pro B	2(40%)	3	5
Total	38	203	241

Chi Sq=7.03 and p=0.008

Incidence of CNS disease was higher in T call ALL (38%) compared to Pre B ALL (12%). Higher incidence of CNS disease in biphenotypic ALL and Pro-B ALL is because of smaller number of cases in these groups.

Table 9: Age of children with CNS disease

N= 38

Age group	CNS disease Present
<1yr	0
1-5 yrs.	23/130 (18%)
6-10 yrs.	10/78 (13%)
11-15 yrs	5/31 (16%)
Total	38

There was no difference in the incidence of CNS disease in the three age groups.

Table 10: WBC at presentation vs CNS disease

	CNS disease Present	CNS disease absent	Total
WBC < 20,000	14 (93%)	1	15
WBC 20,000 - 1,00,000	12 (6%)	175	187
WBC >100,000	12 (30%)	27	39
Total	38	203	241

Chi sq = 10.79 p=0.005

Table 11: WBC count vs CNS disease vs type of ALL

	CNS disease Present	Type of ALL
WBC < 20,000	14	Pre B – 12 Bi-phenotypic - 2
WBC 20,000 - 1,00,000	12	Pre B – 11 Pro B - 1
WBC >100,000	12	Pre B – 1 T cell - 9 Bi-phenotypic – 1 Pro B - 1
Total	38	

When we compared WBC count and type of leukaemia in children with CNS disease, it was found that in children with WBC<100,000/c.mm. Pre B ALL was the most common type of leukaemia. In the high WBC group, T cell ALL accounted for 75% of cases.

Table 12: Cytogenetic analysis

N=158

Cytogenetic profile was available for 158 children in this group. Only numerical abnormalities are depicted here.

	Normal	Hyper-diploidy	Hypo-diploidy	Total
Pre B	49 (38%)	74 (57%)	7 (5%)	130
T cell	13 (59%)	8 (36%)	1 (5%)	22
Bi-phenotypic	0	2	0	2
Pro B	1	3	0	4
Total	63(40%)	87(55%)	8(5%)	158

Overall, 40% of children had normal karyotype and 55% had hyperdiploidy. Hypodiploidy was seen only in 5% of cases. Further break up of type of ALL showed 57% of Pre B ALL cases had hyperdiploidy.

Table 13: Risk stratification

Children were stratified into three risk groups based on various parameters at diagnosis as well as response to treatment. 25% of children had high risk disease.

N = 241.

	Frequency	Percentage
Standard risk	80	33%
Intermediate risk	101	42%
High risk	60	25%
Total	241	100%

Table 14: Risk Stratification vs Type of ALL

It was interesting to note that only children with Pre B ALL were in the standard risk group.

65% of T ALL cases had high risk disease.

	Standard Risk	Intermediate Risk	High risk	Total
Pre B	80 (41%)	82 (42%)	32 (17%)	194
T cell	0	12 (35%)	22 (65%)	34
Bi-phenotypic	0	6 (75%)	2 (25%)	8
Pro B	0	1 (20%)	4 (80%)	5
Total	80	101	60	241

N=241.

Nutritional Status of Children

Nutritional Status of Children at diagnosis (N= 227):

Of the 241 children included in the study, 14 children were < 2 years of age and therefore had to be excluded from the BMI analysis at diagnosis. Thus data of 227 children were analysed for nutritional status. BMI was calculated from the recorded height and weight.

Children were stratified as under-nourished (UN), well-nourished (WN) ,over-weight (OW) and obese(Ob) using CDC BMI centile chart.

Flow chart

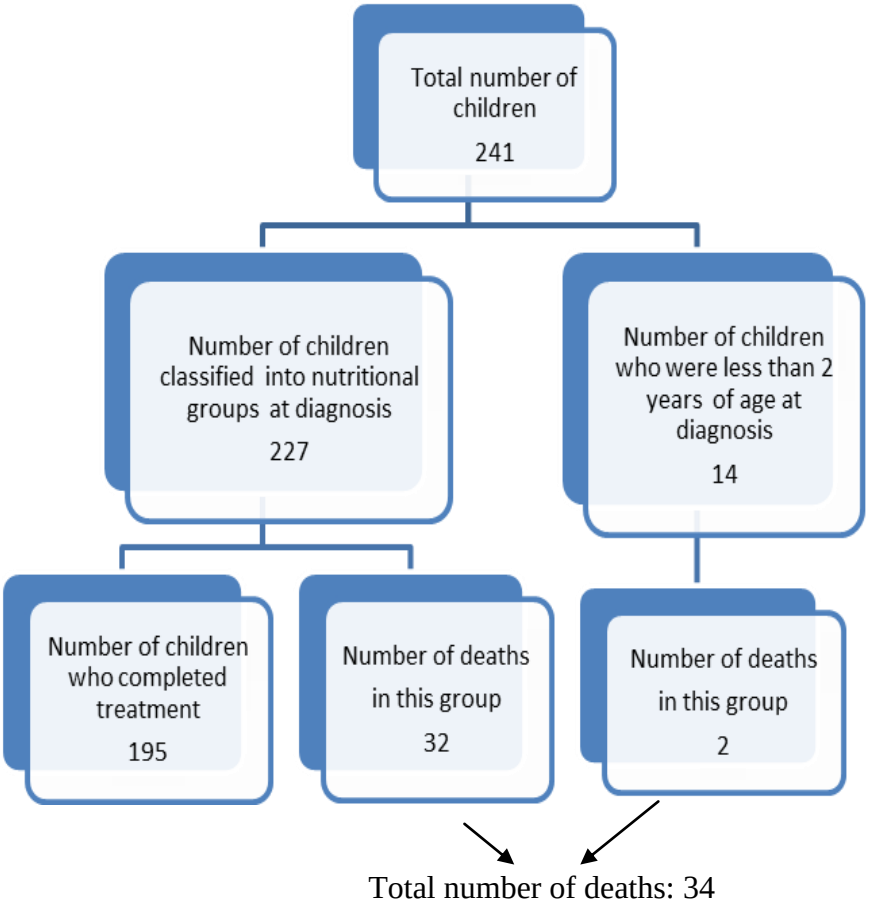
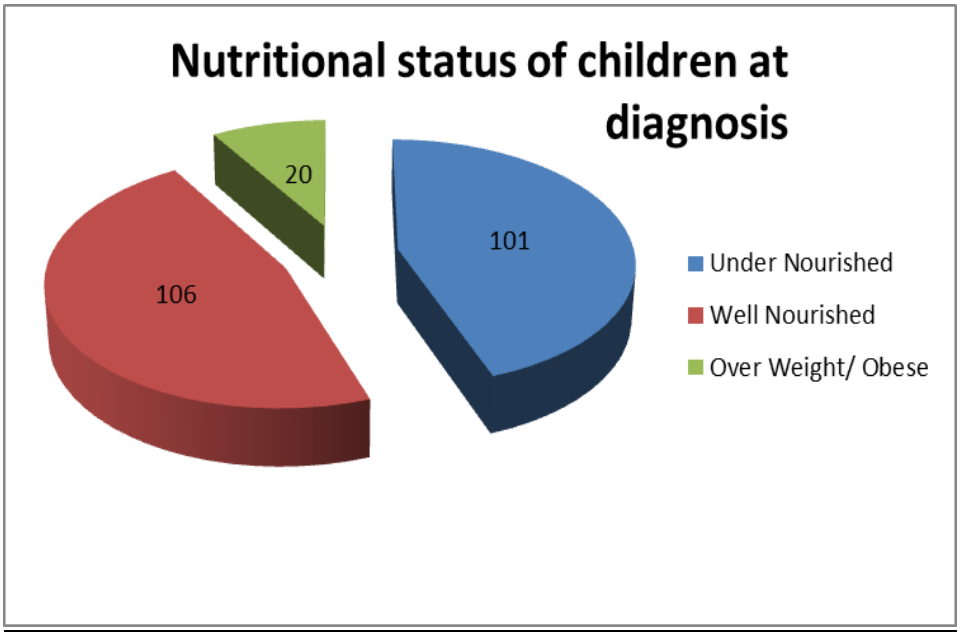


Table 15: Nutritional status at diagnosis (N=227)

	No. of children	Percentage (%)
Under Nourished	101	44
Well Nourished	106	47
Overweight / Obese	20	9
Total	227	100%

Figure 7: Nutritional status at diagnosis



The table and pie chart show nutritional status of children at diagnosis, based on BMI. 47% of children were well nourished and 44% were under nourished. 9% were Obese/overweight.

Table 16: Nutritional Status at diagnosis vs Gender:

	Boys	Girls	Total
Under Nourished	65 (43%)	36 (46%)	101
Well Nourished	73 (48%)	33 (44%)	106
Overweight / Obese	14 (9)	6 (10%)	20
Total	152	75	227

There was no difference in the nutritional status between boys and girls in our study population.

Figure 8: Nutritional status at diagnosis vs Gender

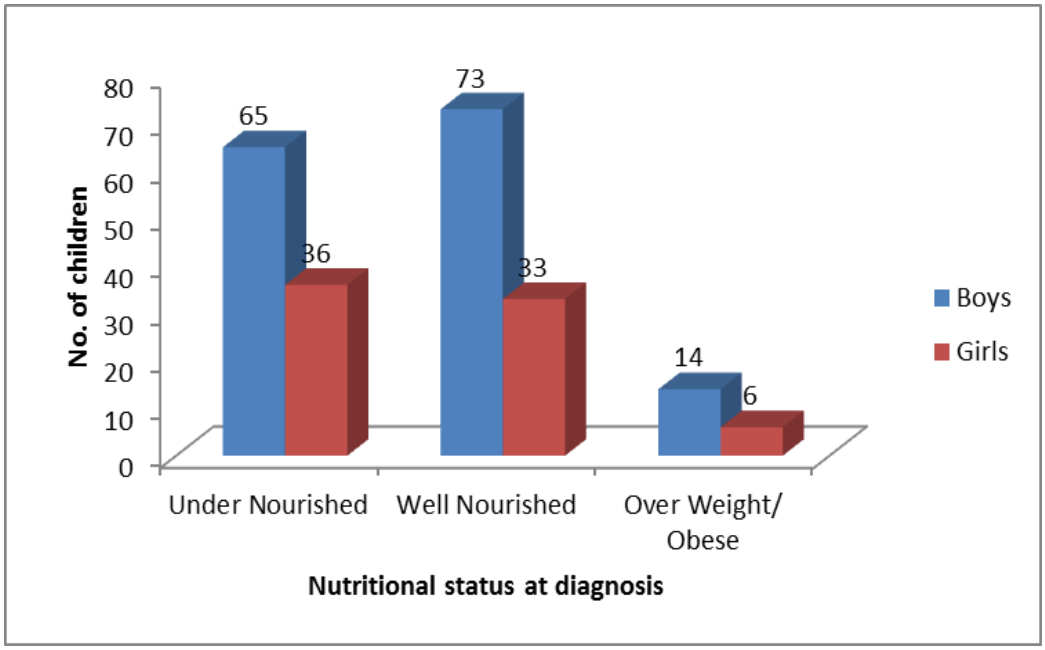


Table 17: Nutritional status at diagnosis vs Age and Gender of the children

N = 227

Gender	Age Group	Under Nourished	Well Nourished	Over Weight/ Obese
Boys (150)	1- 5 yrs* (78)	30 (39%)	40 (51%)	8 (10%)
	5-10 yrs (51)	24 (47%)	23 (45%)	4 (8%)
	10-15 yrs (21)	12 (57%)	8 (38%)	1 (5%)
Total	**150**	**66(44%)**	**71(48%)**	**13(8%)**
Girls (77)	1-5 yrs (40)	16 (40%)	20 (50%)	4 (10%)
	5-10 yrs (27)	17 (63%)	10 (37%)	0
	10 -15yrs (10)	2 (20%)	6 (60%)	2 (20%)
Total	**77**	**35(45%)**	**36(46%)**	**6(8%)**

*In this group 14 children were excluded from analysis as they were less than 2 years of age.

When we compared nutritional status with age and gender, the distribution of cases were similar in all groups.

Table 18: Nutritional status at diagnosis vs type of ALL:

N = 227

	Under Nourished	Well Nourished	Over Weight/Obese	Total
Pre B	77 (42%)	90 (49%)	16 (9%)	183
T cell	19 (58%)	11 (36%)	3 (6%)	33
Bi-phenotypic	3 (50%)	2 (33%)	1 (17%)	6
Pro B	2 (40%)	3 (60%)	0	5
Total	101	106	20	227

There was no difference in the distribution of nutritional groups between different types of leukaemia.

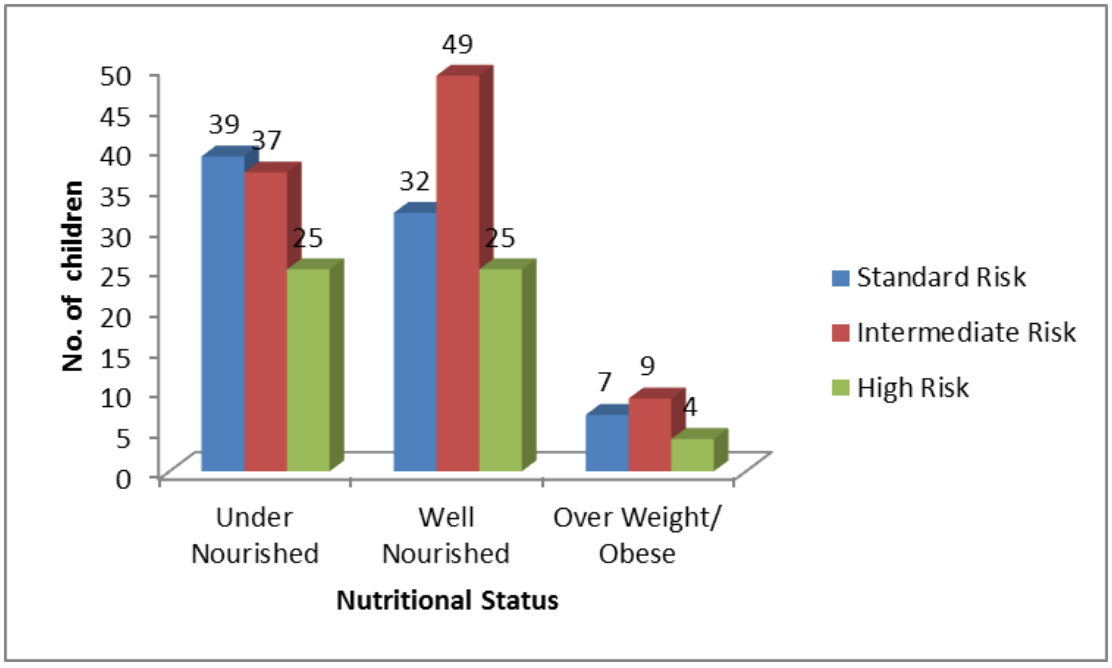
Table 19: Nutritional status at diagnosis vs Risk group

N=227

	Standard Risk	Intermediate Risk	High risk	Total
Under Nourished	39 (39%)	37 (36%)	25 (25%)	101
Well Nourished	32 (30%)	49 (47%)	25 (37%)	106
Over weight/ Obese	7 (37%)	9 (42%)	4 (21%)	20
Total	78	95	54	227

The distribution of cases in the three risk groups were similar in terms of their nutritional status as shown in the table and bar diagram

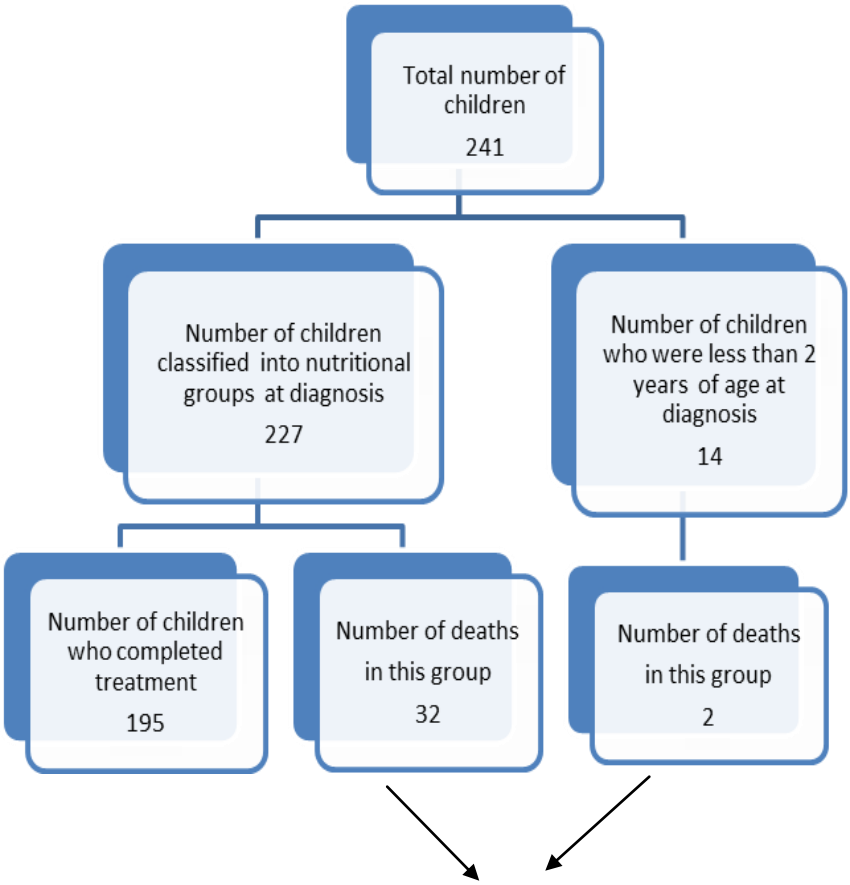
Figure 9: Nutritional status at diagnosis vs Risk group



Longitudinal assessment of nutritional status from diagnosis through treatment and post treatment follow up period.

Of the 227 children included in this study, 34 children died due to various reasons during treatment. 195 completed treatment. In this part of the study, evaluated their nutritional status during and after completion of therapy, impact of nutritional status on response to treatment and complications

FLOW CHART



Total number of deaths -34

Table 20: Nutritional status of children from diagnosis till end of treatment

N = 195

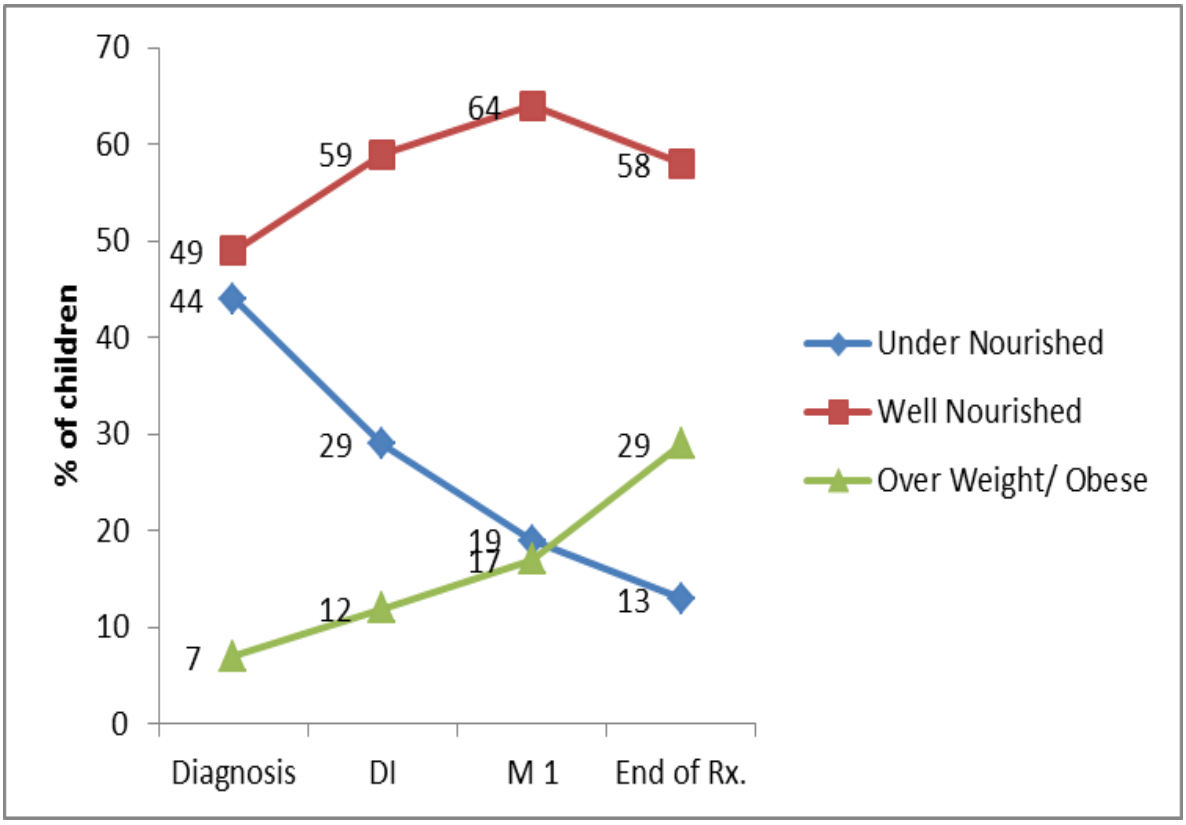
	Diagnosis	DI	M1	End of Rx
Under Nourished	85 (44%)	57 (29%)	37 (19%)	25 (13%)
Well Nourished	96 (49%)	114 (59%)	125 (64%)	113 (58%)
Over weight/ Obese	14 (7%)	24 (12%)	33 (17%)	57 (29%)

P = < 0.05

DI-delayed intensification,

M1- beginning of maintenance

Figure 10: Change in Nutritional status of children from diagnosis till end of treatment



The above table depicts the changes in BMI centile along the course of treatment. Under nourished children tend to decrease in number along the course. 44% were undernourished at diagnosis, 29% during DI, 19 % during beginning of maintenance and only 13% remained in the same group at the end of treatment. Children who were well nourished either remained well- nourished or move to the overweight/obese group. Only 7% of the children were over-weight/obese at diagnosis but by the end of treatment 29% moved to this group.

Analysing the number of children in relation to nutritional status from diagnosis to end of treatment, 85 children were undernourished at diagnosis-23 remained the same,51 became well- nourished and 11 became overweight/obese. Among the 96 children who were well nourished at diagnosis, 59 remained the same, 2 became undernourished and 35 moved to the overweight/obese group. Among the 14 overweight/obese children at diagnosis, 11 remained the same and 3 became well nourished.

We further analysed the data to see at which point children moved from a lower to a higher nutritional status for example from under-nourished to well- nourished and well- nourished to overweight/obese group.

Point 1 –from beginning of induction to beginning of delayed intensification

85(44%) children were undernourished at diagnosis, 32(38%) moved to the well-nourished group and 2(2%) to the overweight/obese group.

96 (49%) children were well-nourished at diagnosis out of which 9(9%) children moved to the overweight/obese group while 70(73%) remained in the same group.

Point 2- from beginning of induction to beginning of maintenance

85(44%) children were undernourished at diagnosis, 44(52%) moved to the well-nourished group and 5(6%) to the overweight/obese group.

96 (49%) children were well-nourished at diagnosis out of which 17(18%) children moved to the overweight/obese group while 51(53%) remained in the same group.

Hence this shows that it is more likely that children tend to move to higher nutrition status by the beginning of maintenance.

Table 21: Nutritional Groups at diagnosis vs end of treatment

	Diagnosis	End of Treatment
Under Nourished	85(44%)	25(13%)
Well Nourished	96(49%)	113(58%)
Over weight / Obese	14(7%)	57(29%)
Total	195	195

N = 195.

Chi. Sq. = 48.4

p = <0.05

23 children in the UN group remained so at the end of treatment and 2 children in the WN group moved into the UN group at the end of the treatment. The vast majority of children (87%) remained well- nourished or improved their , nutrition status during treatment.

Figure 11: At diagnosis vs end of treatment

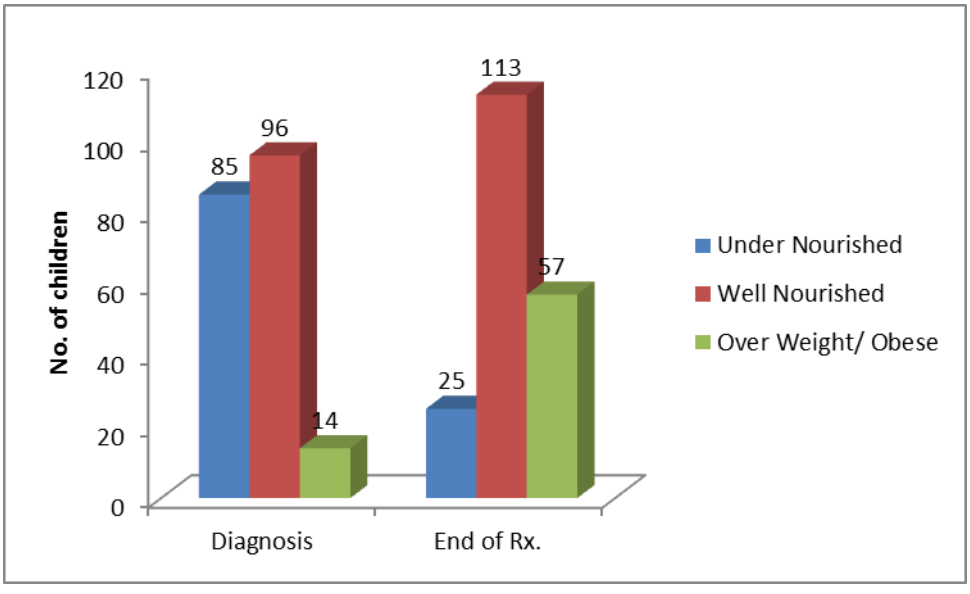


Table 22: Nutritional Groups at end of treatment vs at 1yr follow up

Out of 195, 185 children came for follow up at 1 year.

At 1st year follow up / At end of Treatment	Under Nourished	Well Nourished	Over Weight / Obese	Total
Under Nourished 25	16 (64%)	8 (32%)	1 (4%)	25
Well Nourished 107	7 (7%)	89 (83%)	11 (10%)	107
Over Weight / Obese 53	2 (4%)	9 (17%)	42 (79%)	53
Total=185				**185**

N = 185.

p = <0.05

The above table depicts the change in weight from end of treatment to 1 year follow up.Most of the children from the well nourished group remained in the same group. The percentage of children who became overweight/obese has increased.

Table 23: Nutritional Groups at end of treatment vs at 2yr follow up

At 2nd year follow up / At end of Treatment	Under Nourished	Well Nourished	Over Weight / Obese	Total
Under Nourished 19	13 (68%)	6 (32%)	0	19
Well Nourished 84	8 (10%)	60 (71%)	16 (19%)	84
Over Weight / Obese 42	0	6 (14%)	36 (86%)	42
Total= 145				145

N = 145.

Chi. Sq. = 114.4

p = <0.05

The above table shows the similar change in weight from end of treatment to 2 year follow up. By the end of 2nd year, there were no undernourished children. All had moved to the well -nourished group or the overweight/obese group.

Table 24: Nutritional Groups at end of treatment vs at 3yr follow up

At 3 year follow up / At end of treatment	Under Nourished	Well Nourished	Over Weight / Obese	Total
Under Nourished 10	5 (50%)	5 (50%)	0	10
Well Nourished 48	2 (4%)	32 (67%)	14 (29 %)	48
Over Weight / Obese 23	0	2 (14%)	21 (86%)	23
Total =81				81

N = 81.

Chi. Sq. = 62.30

p = <0.05

The Table shows that none of the children were undernourished at 3 year follow up. By the end of the 3rd year 86% of the children were in the overweight/obese group.

Table 25: Nutritional Groups at end of treatment vs at 5yr follow up

At 5 year follow up / At end of Treatment	Under Nourished	Well Nourished	Over Weight / Obese	Total
Under Nourished 6	4 (66.7%)	2 (33.3%)	0	6
Well Nourished 17	1 (5.9%)	13 (76.5%)	3 (17.66 %)	17
Over weight / Obese 11	0	2 (18.2%)	9 (81.8%)	11
Total – 34				34

N = 34.

Chi. Sq. = 31.56

p = <0.05

Table 26: Nutritional status of children from diagnosis till last follow up

Nutritional Status	At diagnosis	End of treatment	First yr. follow up	Second yr. follow up	Third yr. follow up	Fifth yr. follow up
Under Nourished	85 (44%)	25 (13%)	21 (11%)	21 (14%)	7 (9%)	5 (15%)
Well Nourished	96 (49%)	113 (58%)	106 (47%)	72 (50%)	39 (47%)	17 (50%)
Over weight / Obese	14 (7%)	57 (29%)	54 (29%)	52 (35%)	35 (43%)	12 (35%)
Total	195	195	185	145	81	34

The above Table shows close to 70% of the children in the UN group, gained weight during treatment such that the percentage of children in the UN group steadily decreased ($p < 0.05$ between diagnosis and end of treatment). Thereafter this group remained the same up to 2 years post-treatment and once again showed some weight gain.

The nutrition in the WN group remained rather steady from diagnosis till the final follow-up except for some weight gain during the treatment phase. In the OW/Ob group, there was significant ($p < 0.05$) increase in weight such that the percentage of children increased 4 fold in this group by the end of treatment. By 5 years post-treatment the percentage of children in this category stabilised to about 5 fold the number at diagnosis.

Figure 12: Nutritional status of children from diagnosis till 5 years of follow up

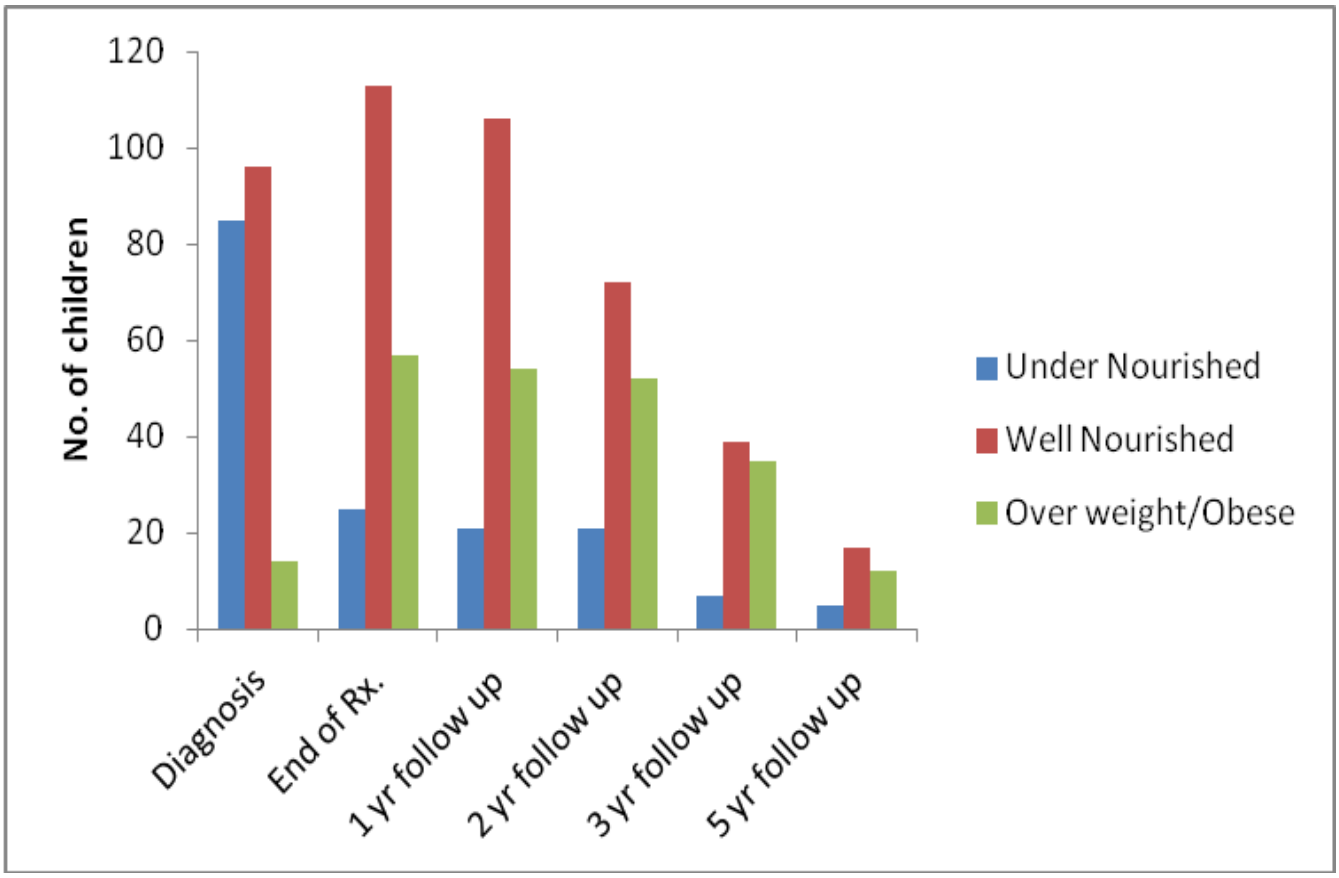


Figure and Table show a gradual increase in weight on follow up in children who completed treatment for ALL. Most of the children are either well nourished or overweight/obese as early as the 1st and 2nd year of follow up.

Impact of Nutritional Status on response to treatment in children with ALL

Table 27: Nutritional Groups vs Early response (Early response to Rx. – Day 8 blast count)

N-227

	GPR	**PPR**	Total
Under Nourished	88	13 (13%)	101
Well Nourished	101	6 (6%)	107
Over Nourished /Obese	18	1 (5%)	19

p = 0.955 chi. sq.= 0.09

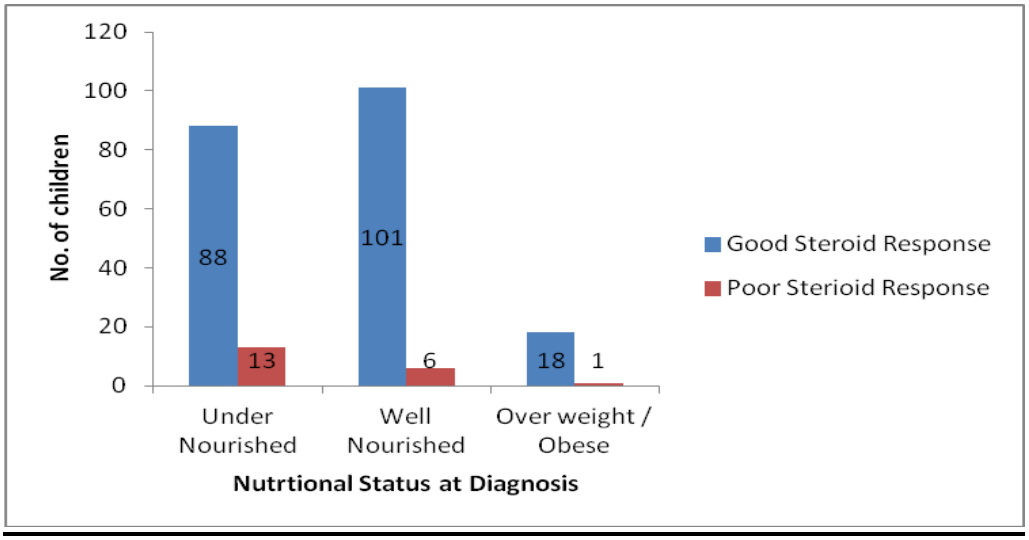
GPR – Good prednisolone response - Day 8 blast count < 1000

PPR- poor prednisolone response - day 8 blast count > 1000

Of the 20 children who had PPR, 14 were high risk, 5 were intermediate risk and

1 belonged to the standard risk group.

Figure 13: Nutritional Groups vs early response



Predominantly children in the undernourished group had PPR .

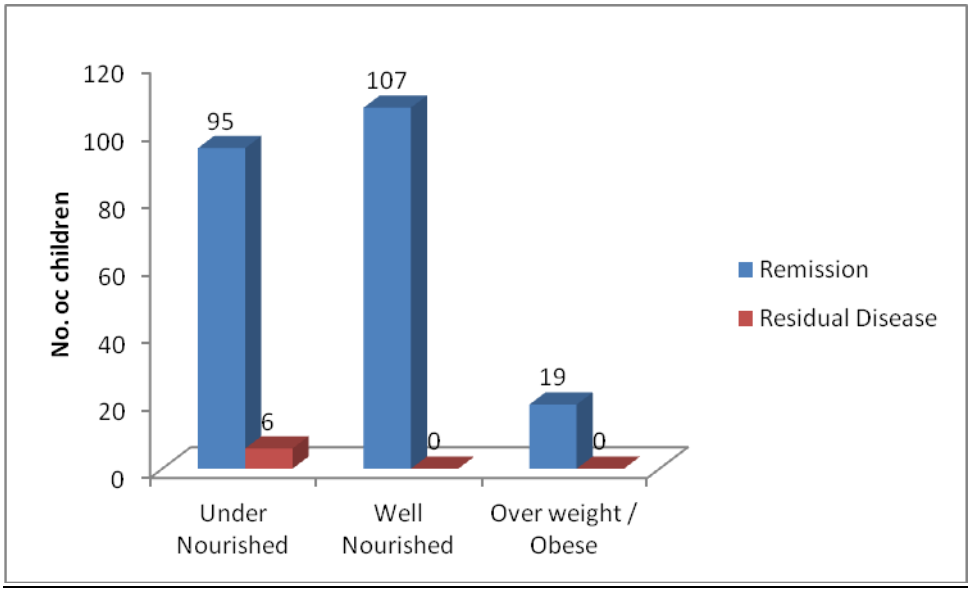
Table 28: Nutritional status at diagnosis vs Bone marrow response to treatment – Day 14 blast percentage

N = 227

	Remission	**Residual Disease**	Total
Under Nourished	95	6	101
Well Nourished	107	0	107
Over Nourished /Obese	19	0	19

P = 0.215

Figure 14: Nutritional status at diagnosis vs Bone marrow response



The above figure shows that 6 children in the under nourished group had residual disease on day 14 bone marrow.Of the 6 children,5 belonged to the high risk group and 1 child had intermediate risk.

Table 29: BMI vs Bone Marrow Remission(Bone marrow remission at day 35 (end of induction)

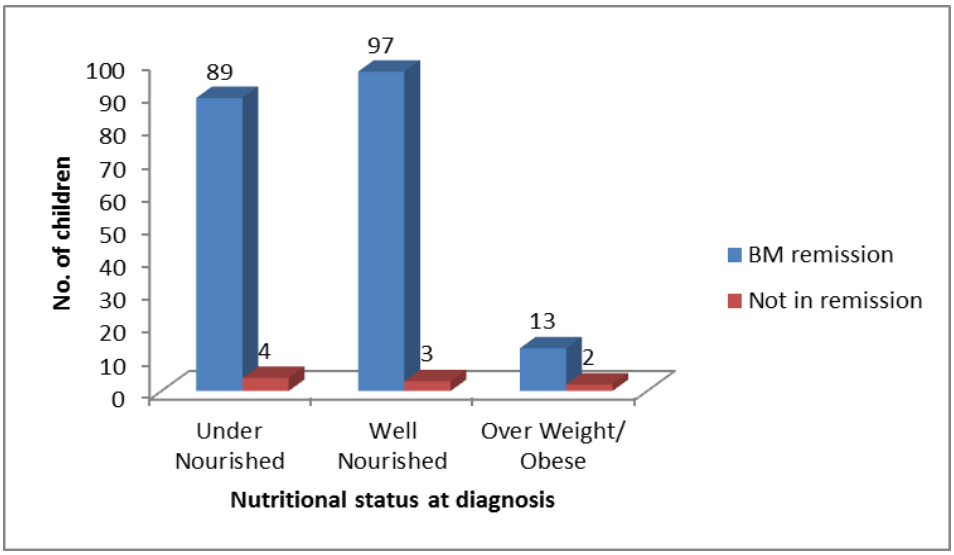
	BM Remission	**Not in Remission**	Total
Under Nourished	89	4 (4%)	93
Well Nourished	97	3 (3%)	100
Over Nourished / Obese	13	2 (13%)	15
Total	199	9*	208

(p = 0.186)

*Totally there were 10 children with residual disease, only 9 of them were analysed, as one of them was < 2 years of age at diagnosis.

Of the 10 children, 7 were from the high risk group, and 3 from intermediate group

Figure 15: BMI vs Bone Marrow Remission(end of induction)



There was no significant difference in the end of induction remission in relation to the nutritional groups.

Table 30: Nutritional status at diagnosis vs Febrile neutropenia episodes during treatment

This data was available for 215 children.

	0	1	2	3	4	5	6	7	Total
Under Nourished	17	25	20	18	10	5	1	0	96
Well Nourished	19	30	24	16	11	0	1	0	101
Over weight / Obese	3	6	5	1	2	0	0	1	18
Total	39	61	49	35	23	5	2	1	215

(p = 0.135)

\

Table 31: Nutritional status at diagnosis vs Febrile neutropenia episodes during treatment

N-215

Clubbing the number of febrile neutropenia episodes into 0-3 episodes and > 3 episodes

	0-3 episodes	4-7 episodes	Total
Under nourished	80	16	96
Well nourished	89	12	101
Overweight/obese	15	3	18

Table 31 showed no significant difference found in the number of episodes of febrile neutropenia in relation to the nutritional status of children at diagnosis.

4 children who had no febrile neutropenia episodes relapsed.

Table 32: Nutritional status at diagnosis vs Relapse and time of relapse

	Relapse during treatment	Relapse after treatment
Under Nourished (85)	2	4
Well Nourished (95)	2	6
Over weight/ Obese (14)	0	1
Total (195)	4	11

15/ 195 children relapsed- 4 during treatment and 11 after completion of treatment.

There was no significant difference in the number of children relapsed between different nutritional groups.

Table 33: Nutritional status(at diagnosis) of children who died during treatment

34 children died during treatment. For the purpose of analysis we divided them into two groups; well nourished and not-well nourished. The not –well nourished group included both under nourished and overweight/obese.

	Dead	Alive	Total
Well Nourished	11 (10%)	96 (90%)	107
Not - Well Nourished	21 (18%)	99 (82%)	120
Total	32*	195	227

($p = 0.09$)

*2 patients were excluded in the above table as they were less than 2 years of age at diagnosis and hence BMI could not be analysed.

10% of well nourished and 18% of not-well nourished died.

There was no statistically significant difference between the groups, probably because the numbers were small and also could be that there are many other factors contributing to their death.

Table 34: Nutritional status at diagnosis vs Phase of treatment at death

	Ind	Con.	DI 1 1	DI 2 1	DI 2 2	IM 1	IM 2	Maint.	Total
Under Nourished	8	1	3	0	1	0	1	2	16
Well Nourished	6	0	1	2	0	1	0	1	11
Over weight / Obese	5	0	0	0	0	0	0	0	5
Total	19	1	4	2	1	1	1	3	32

($p = 0.585$)

Ind - Induction

Con - Consolidation

DI -Delayed Intensification

IM - Interim Maintenance

M - Maintenance

*2 patients were excluded in the above table as they were less than 2 years of age at diagnosis and hence BMI could not be analysed

The above table shows the phase of treatment when these children died. 19/34 (59%) children died during induction phase of treatment. There didn't seem to be any correlation between nutritional status and mortality.

Table 35: Risk stratification at diagnosis vs death

	Dead	Alive	Total
Standard risk	10 (30%)	70	80
Intermediate risk	12 (35%)	83	95
High risk	12 (35%)	40	52
Total	34	195	227

($p = 0.084$)

Analysis of the children who died, there was no statistical significance in relation to risk strategy.

Table 36: Risk Stratification at diagnosis vs Phase of chemotherapy at death

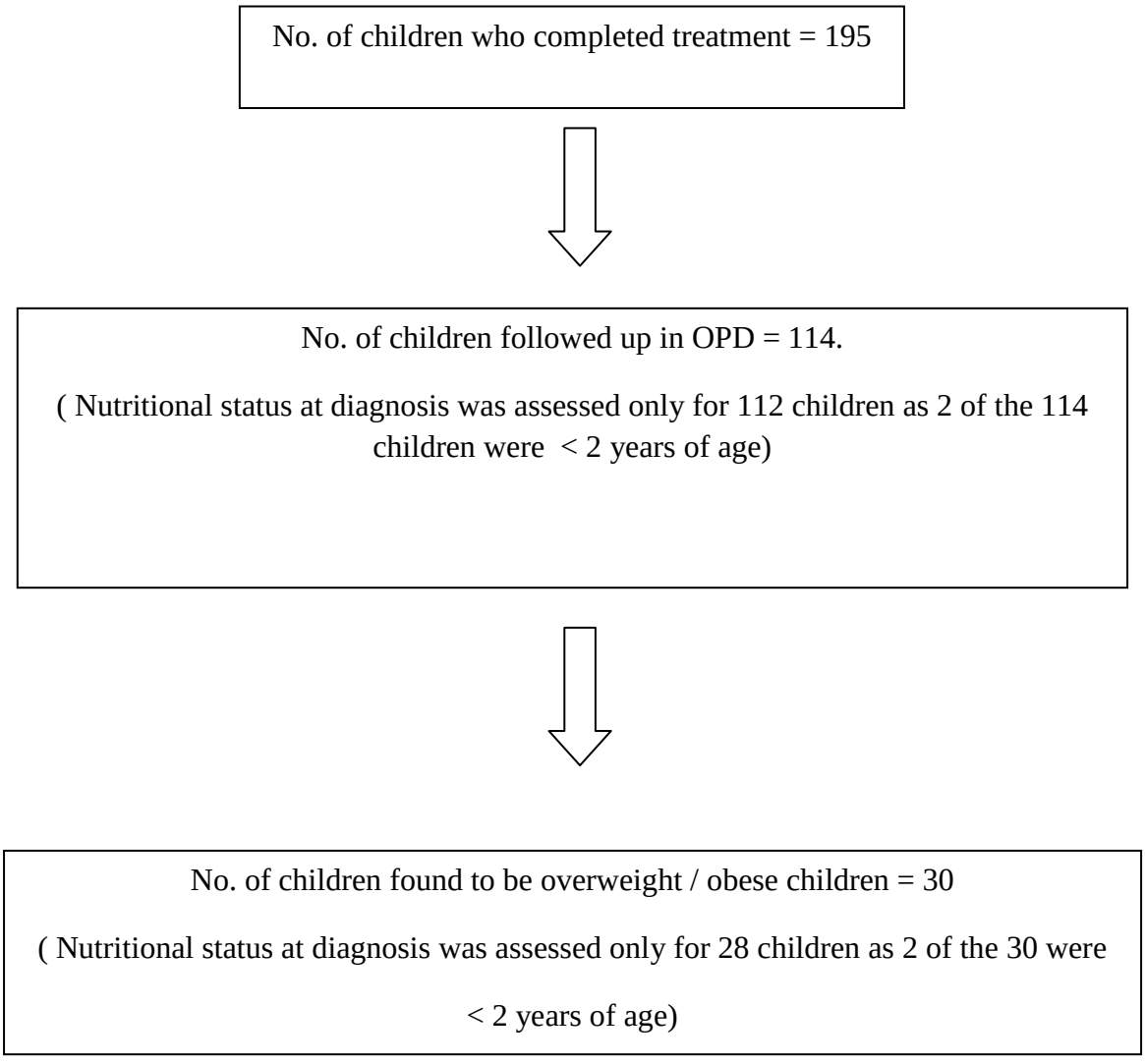
Risk Stratification	Ind	Con.	DI 1 1	DI 2 1	DI 2 2	IM 1	IM 2	Maint.	Total
Standard	6	0	1	1	0	0	0	2	10
Intermediate	6	0	3	1	0	1	0	1	12
High	6	1	1	2	0	1	0	1	12
Total	18	1	5	4	0	2	0	4	34

$p = 0.857$

Cause of death: All the children died due to severe sepsis with febrile neutropenia. Most of them died during the induction phase.

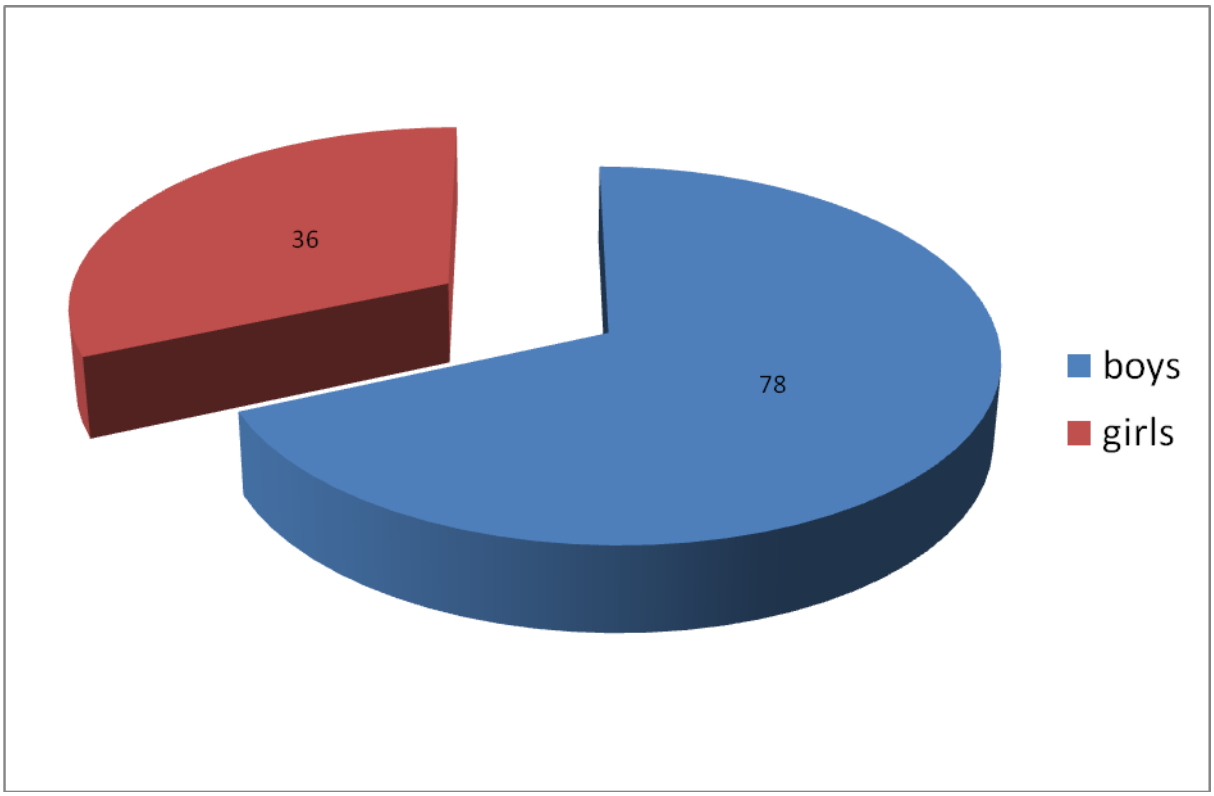
Screening for metabolic syndrome in children who had completed treatment and reviewed during the study period

Of the 195 children who successfully completed treatment 114 children came for review to the outpatient clinic during the study period and were included in this analysis. Their nutritional status was assessed and those who were overweight/obese were screened for features of metabolic syndrome.



Total children followed up in OPD -114, 78 boys and 36 girls.

Figure 16 : Gender distribution at follow up:



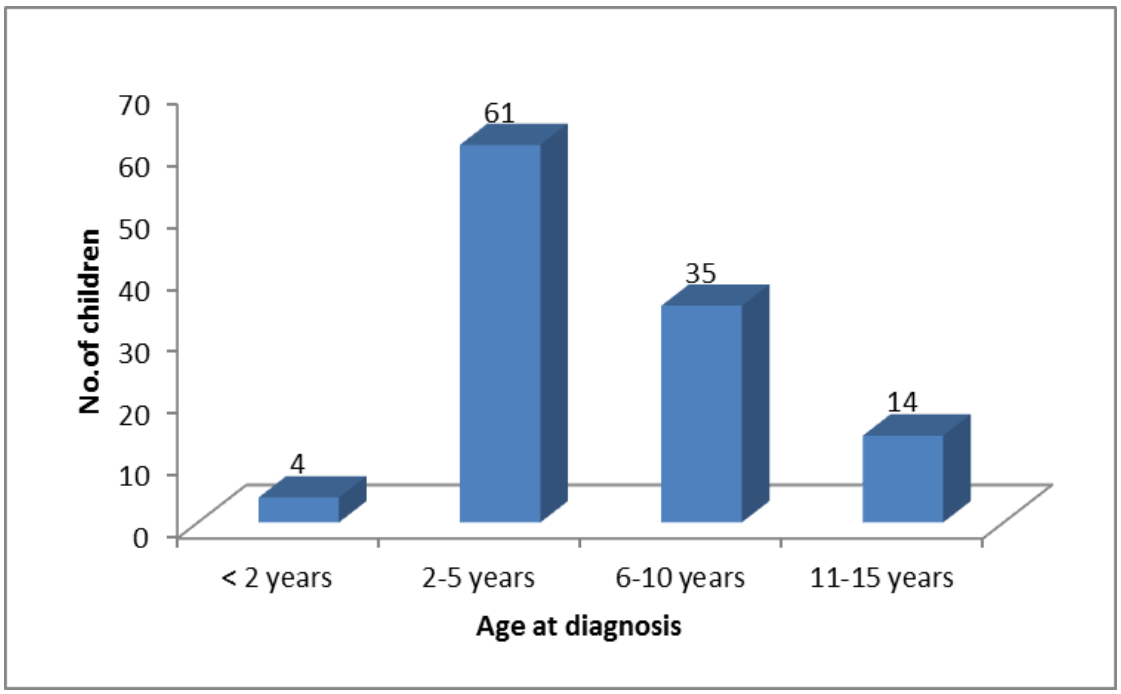
The mean age at diagnosis was 5.8 years (range 11months to 14.3years)

\Table 37: Age distribution at diagnosis

Age	No. of children
< 2 year	4(3%)
2-5 years	61(54%)
6-10 years	35(31%)
11-15 years	14(12%)

Total -114

Figure 17: Age distribution at diagnosis



The above table and graph shows that most of the children belonged to 2 -5 years age group.

Table 38 : Age and Gender distribution at follow up:

	Boys	Girls	Total
< 1 year	2	0	2
1-5 years	45	18	63
6-10 years	20	15	35
11-15 years	11	3	14
Total	78	36	114

The mean follow up of these children after completion of treatment was 2.4 years.(range 3 months to 9 years)

Table 39: Nutritional status at diagnosis vs end of treatment vs follow up.

N=114

	At diagnosis	End of treatment	On follow up
Under nourished	55 (48%)	19 (17%)	5** (4%)
Well nourished	51 (45%)	70 (61%)	81 (71 %)
Overweight/obese	6 (5 %)	25/27 (22%)	28/30 (25%)
Total	112*	114	114

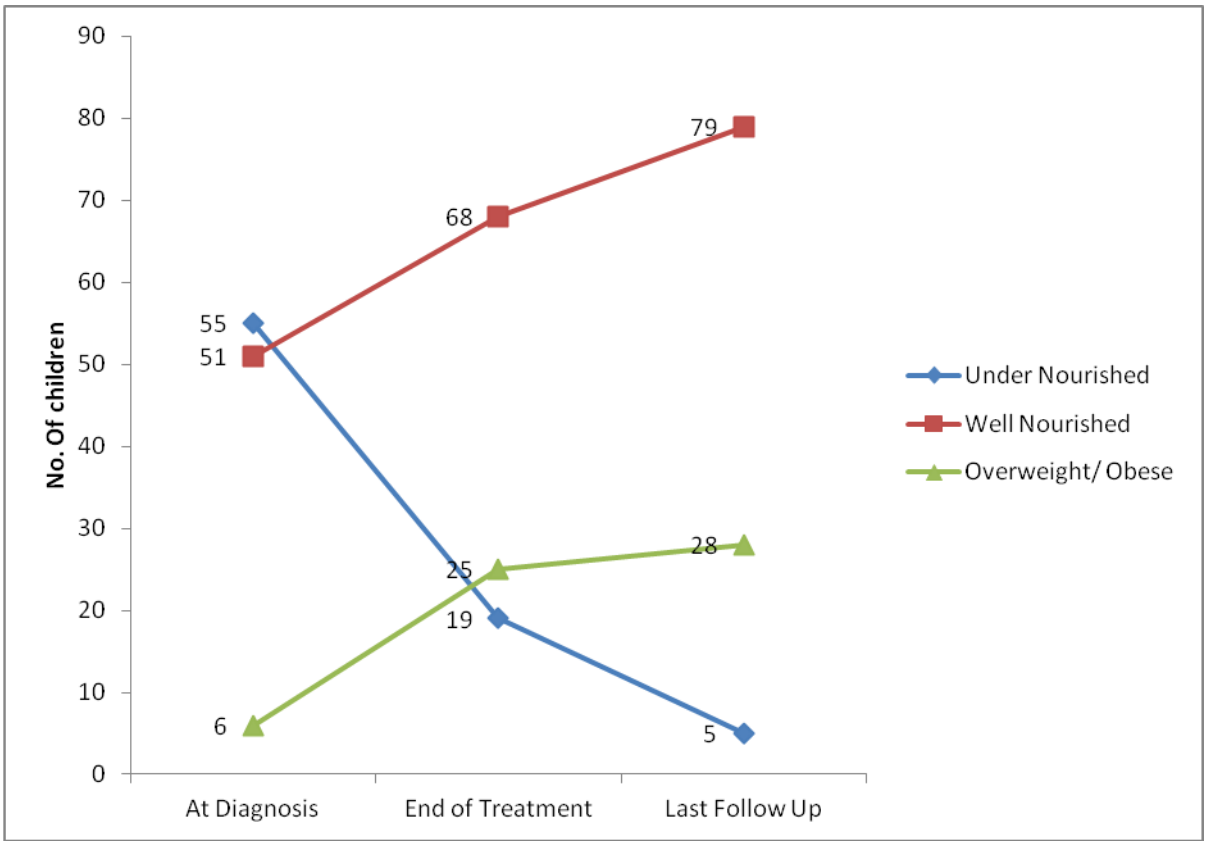
P < 0.005

* 2 children were < 2 years of age at diagnosis, hence their BMI centile was not calculated.

** 5 children in the under nourished group at follow up were undernourished at diagnosis also.

Figure 18: Nutritional status at diagnosis vs end of treatment vs follow up.

N=114



The above figure depicts the change in weight over the course of treatment. At diagnosis ,48% were undernourished, by the end of treatment only 17% remained in this group and at follow up only 4% remained in this group. The percentage of children in the well- nourished group steadily increased. Although the percentage of children in the OW/Ob group significantly increased during treatment, between the end of treatment and follow-up, there was no significant increase in the number of children in this group. Thus most of the increments in BMI occurred during treatment (p value <0.005) and there was no significant change from completion of treatment to follow up.

Analysis of overweight/obese patients at follow up

Thirty children were found to be overweight/obese among those who were followed up during the study period. There were 22 boys and 8 girls. The prevalence of obesity in this group was 26 %.The mean age at follow up was 10.3 years (range 6 years to 15 years).

The age distribution is as follows:

Table 40: Age distribution of overweight/obese children

N=30

Age	No. of children
5-10 years	14(47%)
10-15 years	16(53%)

Mean BMI was 24.1kg/m^2 (range 19.2 to 32.8)

Table 41: Age at follow up, Gender and BMI

Age	Boys	Mean BMI	Girls	Mean BMI
6-10 years	10	23.7	5	21.9
11-15 years	12	25	3	24.7
Total	22		8	

Table 42: Linear growth of the children at follow up

Total no. of Children	Current height centile corresponding to target height	Current height centile >Target height	Current height centile < Target height
30	6(20%)	19(63%)	5(17%)

The above table shows that while 20% of children had height corresponding to their target height, 17% had height centile below the target height. Interestingly 63% children had height above their target range.

The mean duration between completion of treatment and follow up was 2.1 years.(range 3 months to 9 years)

Six children (20%) were in puberty and 24 children (80%) were pre-pubertal as shown below. No one had precocious puberty.

Table 43 : Age vs Tanner stage

	Tanner stage 1 Pre pubertal	Tanner stage ≥ 2
5-10yrs	14(47%)	0
10 -15 yrs	10(33%)	6(20%)

Table 44: Tanner stage vs gender

	Tanner stage 1	Tanner stage ≥ 2
Boys(22)	19	3
Girls(8)	5	3

Comparing their nutritional status at different time points of ALL treatment.

Table 45: BMI - at diagnosis vs during beginning of maintenance (M1) vs end of treatment.

N=30

	Diagnosis	DI	M1	End of Rx.	At follow up
Under Nourished	6	0	0	0	0
Well Nourished	16	17	8	2	0
Overweight/obese	6	11	22	28	30
Total	28*	28*	30	30	30

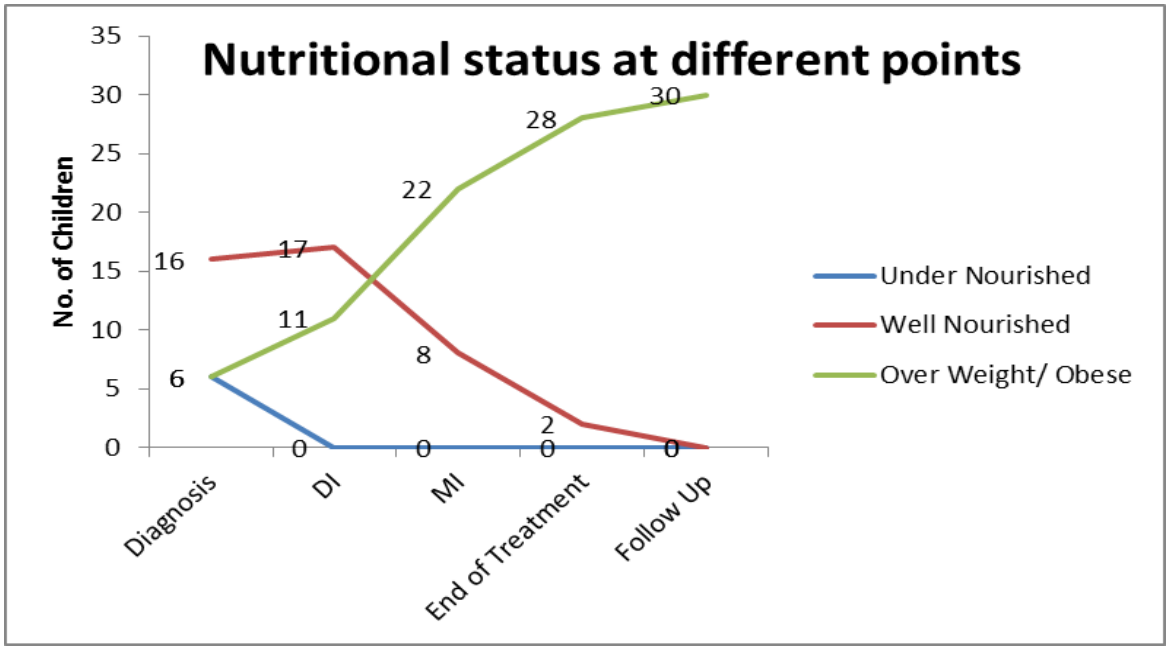
Fisher's exact <0.05

*2 patients were less than 2 years of age at diagnosis.

DI –Delayed intensification

M1 – Beginning of maintenance

Figure 19: BMI - at diagnosis till end of treatment.

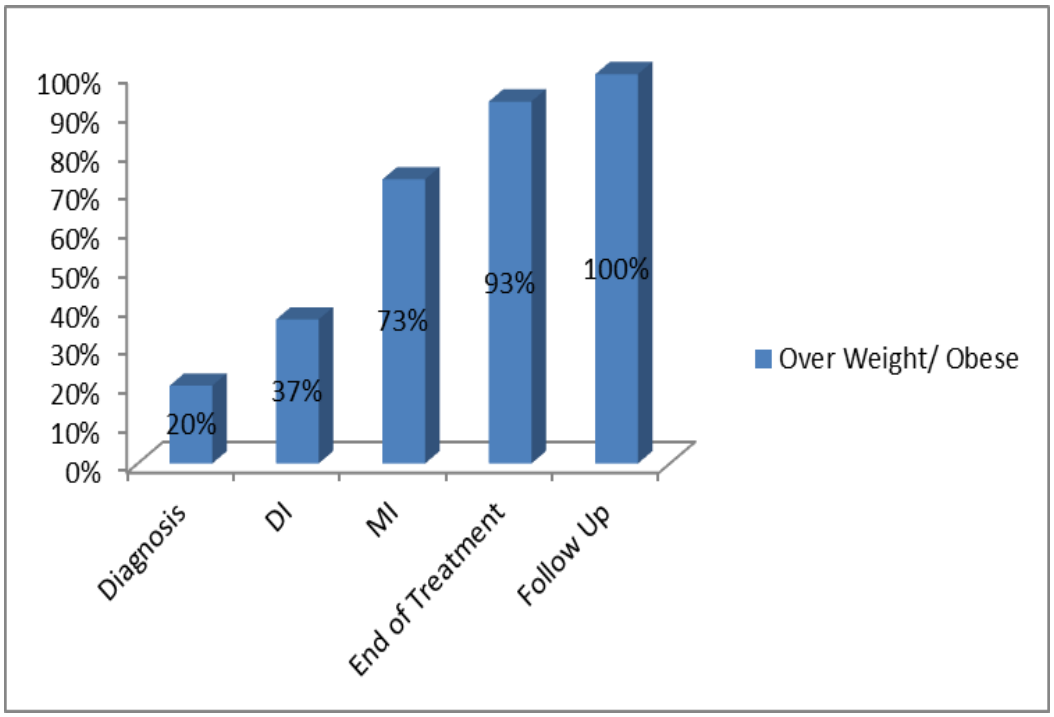


The above graph shows the change in weight of the 30 children during the course of treatment and follow-up.

6 children who were undernourished at diagnosis had caught up in weight by the beginning of delayed intensification phase itself and beyond this phase of treatment none were undernourished. .

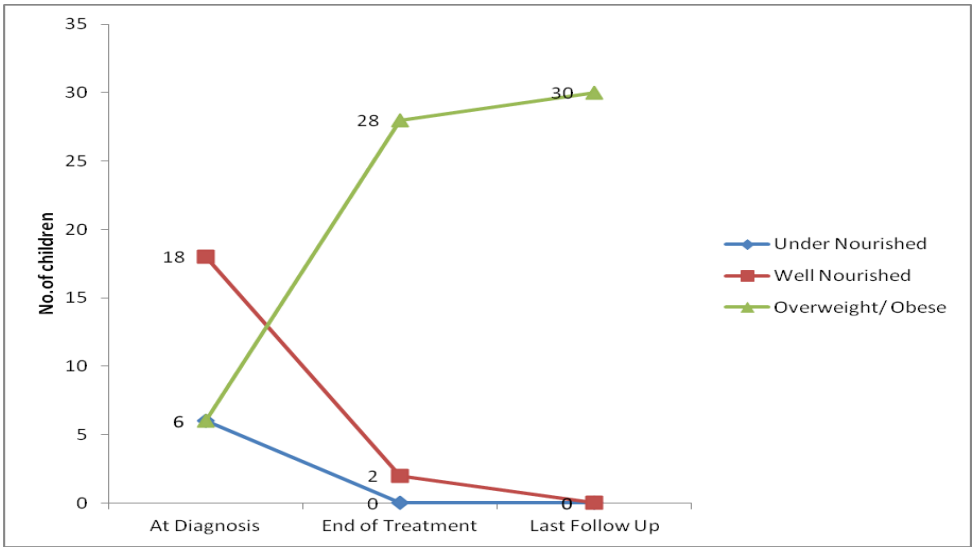
16 children who were well nourished at diagnosis became overweight/obese by the end of treatment and remained so at follow-up. The number of children in the OW/Ob group steadily increased from 6 at diagnosis to 28 at the end of treatment. Only 2 children subsequently moved into this group during follow-up. The increase in BMI was statistically significant ($p < 0.05$).

Figure 20: Cumulative graph showing increase in obesity.



Among those who were overweight/obese at follow up, significant weight gain occurred during the induction phase of treatment such that the numbers doubled by the end of induction phase. By the beginning of maintenance phase close to 80% were obese.

Figure 21: BMI - From diagnosis to final follow up.



The above graph and tables shows that BMI centile is on the increasing trend from diagnosis to the end of treatment and follow up.

Table 46: Progression of weight of the 6 undernourished children who became obese:

	Diagnosis	D.I.	M 1	End of Rx.	Follow Up
1st child	UN	WN	OW	OW	OW
2nd child	UN	WN	OW	Ob	OW
3rd child	UN	WN	Ob	Ob	Ob
4th child	UN	OW	OW	OW	OW
5th child	UN	WN	OW	OW	OW
6th child	UN	WN	WN	OW	OW

UN – Under Nourished

WN – Well Nourished

OW– Over weight

Ob - Obese

DI- Delayed intensification

M1- Beginning of maintenance

Five out of six children were undernourished at diagnosis moved into well- nourished group and one child became overweight by the end of induction phase. By the end of delayed intensification phase five of them had become overweight/obese and remained so till follow up.

Number of children who have received Cranial RT:

Table 47: children who received RT

Cranial irradiation	Frequency	Percentage(%)
Given	6	20
Not Given	24	80
Total	30	100

Only 6(20%) children received cranial irradiation, while 80% did not receive cranial irradiation. Children with definite CNS disease received 18 GY and those with traumatic CSF received 12 Gy .

Children who received Cranial RT were analysed according to their nutritional status from diagnosis to the end of treatment which is shown below.

Table 48: Nutritional status at Diagnosis vs Cranial RT

	Cranial RT Given	Cranial RT Not Given	Total
Under Nourished	2 (33%)	4	6
Well Nourished	3 (18%)	15	18
Over weight/ Obese	1 (17%)	5	6
Total	6	24	30

Fisher's exact = 0.311 RT- radiotherapy

Table 49: Nutritional status at Maintenance vs Cranial RT

	Cranial RT Given	Cranial RT Not Given	Total
Under Nourished	0	0	0
Well Nourished	2 (25%)	6 (75%)	8
Over weight / Obese	4 (18%)	18 (82%)	22
Total	6	24	30

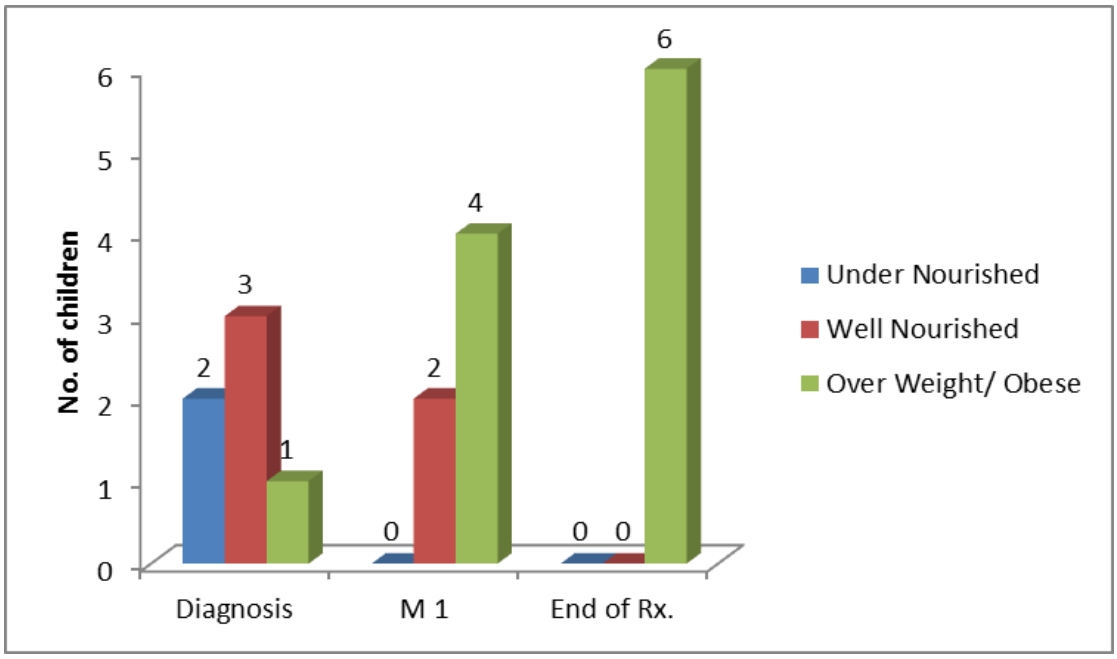
Fisher's exact = 0.217

Table 50: Nutritional status at End of treatment and Follow up vs Cranial RT

	Cranial RT Given	Cranial RT Not Given	Total
Under Nourished	0	0	0
Well Nourished	0	2	2
Over weight / Obese	6 (22%)	22 (78%)	28
Total	6	24	30

Fisher's exact = 0.99

Figure 22: Nutritional status of children (who received Cranial RT) - at diagnosis vs beginning of maintenance vs end of treatment



Analysis of the nutritional status of the children who received cranial Radiotherapy depicts an upward trend towards the overweight/ obese category but was not statistically significant (p=0.99)

Table 51: Relapse

Relapse	Frequency	Percentage(%)
No	29	97
Yes	1	3
Total	30	100

There was only one patient (3.3%) who had CNS relapse, six months after completion of treatment.

Table 52: Blood pressure centile in Overweight/ Obese children.

Blood Pressure	No. of children
Systolic BP >90th centile	1
Systolic BP >95th centile	2
Diastolic BP >90th centile	2
Diastolic BP >95th centile	2

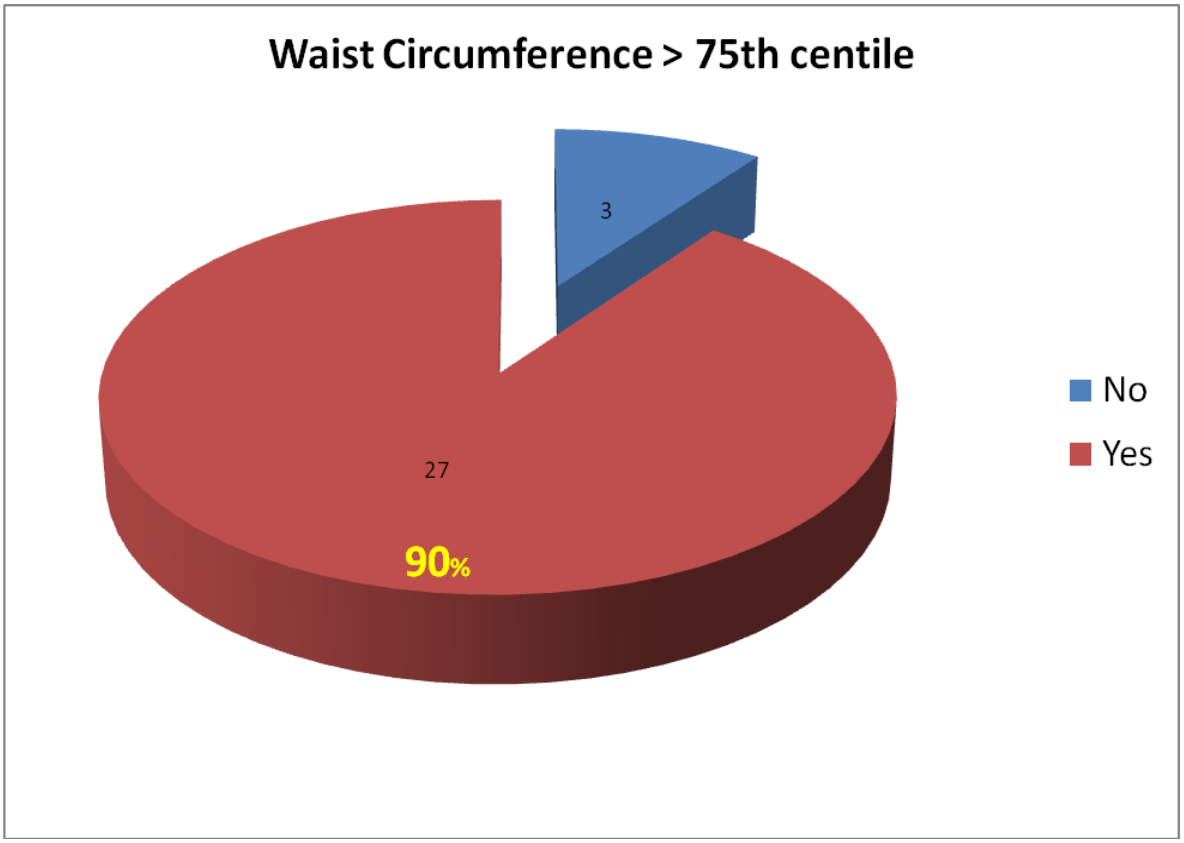
Two children each had systolic and diastolic BP> 95th centile. In addition 10% (3/ 30) of children had SBP and DBP above the 90th centile for age.

The prevalence of hypertension (BP>95th centile) = 13% (4/30).

Table 53: Waist Circumference at follow up:

WC >75th Centile	Frequency	Percentage(%)
No	3	10
Yes	27	90
Total	30	100

Figure 23: Children with waist circumference >75th centile:



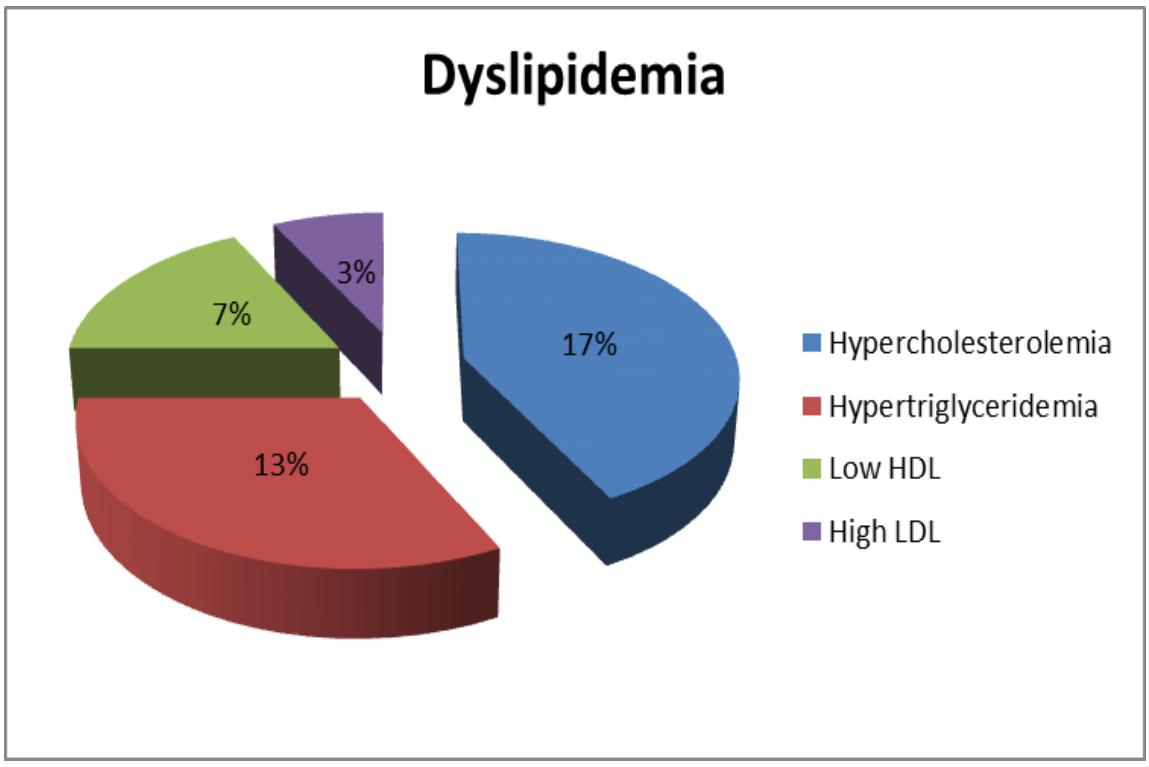
The above graph shows that 90% of the obese children had waist circumference more than 75th centile.

Table 54: Lipid Profile:

N = 30

Lipids	Number of Children	Prevalence (%)
Hypercholesterolemia	5	17
Hyper Triglyceridemia	4	13
Low HDL	2	7
High LDL	1	3

Figure 24: Dyslipidaemia



Concurrent dyslipidaemia :

2 children had both high cholesterol level and high triglyceride level

1 child had elevated cholesterol and high LDL

1 child had high triglyceride and low HDL level.

Glycosylated Haemoglobin

Two children (7%) had elevated HbA1C levels , however their fasting plasma glucose values were in the normal range.

Glucose Insulin Ratio (GIR) :

Six children (20%) had G/I ratio < 5 of which 4 were pre-pubertal and two were pubertal.

Table 55: GIR vs Tanner stage

Tanner stage	Low GIR	Normal GIR	Total
Stage 1	4(15%)	22	26
Stage ≥ 2	2(33%)	2	4
Total	6	24	30

P=0.169

Table 56: Correlation between Lipid profile and Waist Circumference(WC):

Waist circumference>75th centile- 90% (27/30)

N = 27.

	No. of children with WC>75th centile(%)	
Hypercholesterolemia	5(19%)	P =0.99
Hypertrigylceridemia	4(15%)	P =0.99
Low HDL	2(7%)	P =0.99
High LDL	1(4%)	P =0.99
HbA1c	2(7%)	P =0.99
GIR	6(22%)	P =0.99
Parental BMI		
Father's BMI	23(85%)	P =0.24
Mother's BMI	24(89%)	P =0.27

Figure 25: Waist Circumference vs Lipid profile:

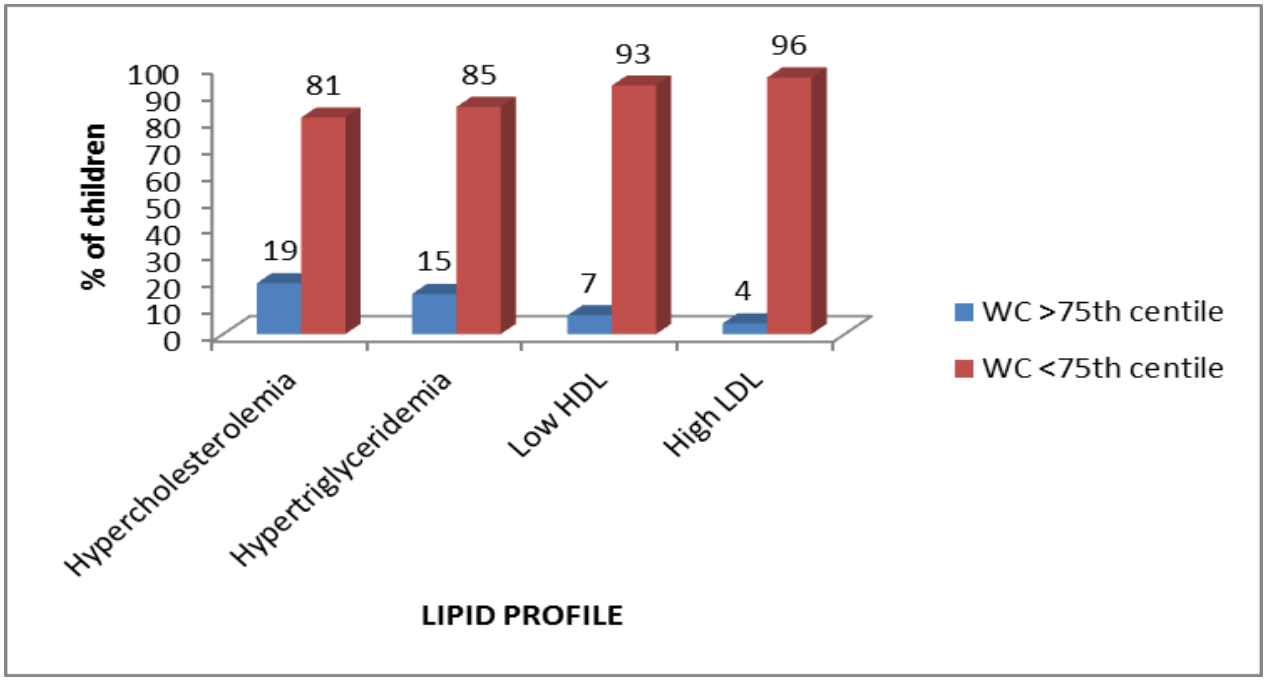
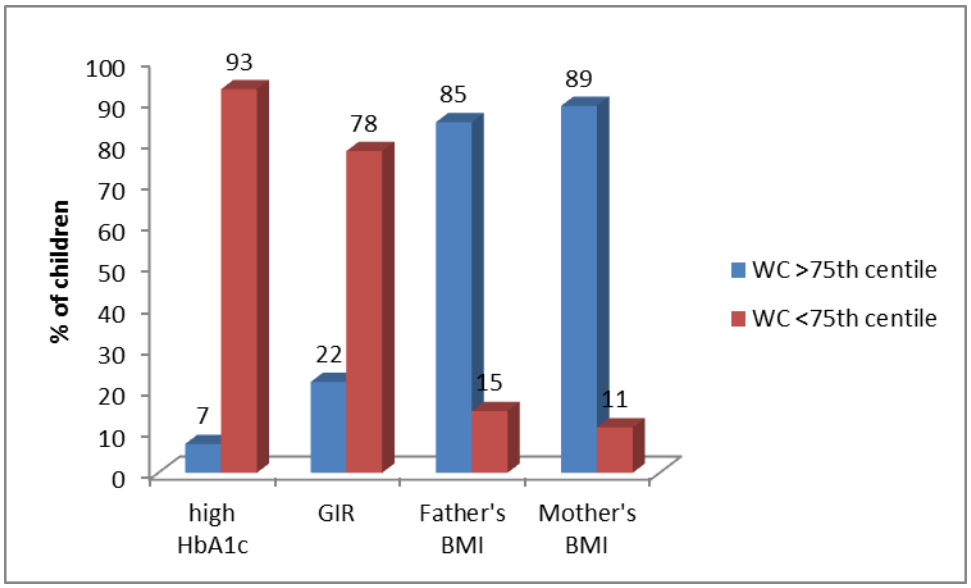


Figure 26: Waist Circumference vs HbA1C, GIR and Parental BMI Centile:



Correlation of waist circumference with lipid profile, HbA1c, GIR and parental BMI did not show statistical significance.

DISCUSSION

DISCUSSION

We studied 241 children treated for acute Lymphoblastic leukaemia. Their clinical profile showed the following (i) male: female ratio was 7:3 (ii) mean age was 5.9 years (11months-15 years) (iii) 55% of the study population was <5years of age at the time of diagnosis. Gender ratio of our study group is tilted towards males, as was seen in an earlier publication from Chandy et al[47]. The age distribution is similar to that reported by Bachir et al[48].

Different types of ALL as per immunophenotype in our study showed Pre-B ALL 81%, T-ALL 14%, Biphenotype ALL 3% and Pro-B ALL 2%. This distribution is similar to that is described in the literature.(48, 49).The incidence of CNS disease was 16%; with a higher incidence among those with T-ALL (38%) This appears to be much higher than several other studies (47,50) probably because only 30% of children treated in our unit was included for this study and hence it may not be a true representation. As per our risk stratification criteria, 1/3 rd had standard risk and 25% had high risk disease. Among those with T-ALL 65% had high risk disease and the remaining had intermediate risk disease.

Based on BMI, Children were stratified as under-nourished (UN), well-nourished (WN),over-weight (OW) and obese(Ob) using CDC BMI centile chart. The overweight and obese were grouped as a single group for further analysis. After excluding 14 children who were less than 2 years of age at diagnosis, therefore ineligible for analysis based on BMI, 227 children were divided into various groups based on their nutrition. 44% of children were undernourished and 9% were overweight/obese. The prevalence of under nutrition and obesity in our study was comparable to that published by others, where 50% was undernourished and 8% were obese (6,8,34)

Longitudinal assessment of nutritional status from diagnosis through treatment and post treatment follow up period

195 children who had completed treatment and on follow up (mean 2.6 years, range 3 months- 9.6 years) were included in this part of the analysis. We found a statistically significant trend towards increasing BMI from diagnosis through treatment and post treatment period (Table 26). 44% of children were under nourished at diagnosis and at the end of treatment only 13% remained under nourished. In contrast, the proportion of obese children went up from 7% at diagnosis to 29% at the end of treatment. This change in BMI in our patients was statistically significant ($p<0.05$).

We further analysed the change in nutritional status at different time points. Change of BMI from beginning of induction to beginning of delayed intensification shows that 85 children were undernourished at diagnosis, 32(38%) moved to the well-nourished group and 2(2%) to the overweight/obese group. Of the 96 children who were well-nourished at diagnosis, 9(9%) moved to the overweight/obese group while 70(73%) remained in the same group. Nutritional change from beginning of induction to beginning of maintenance shows that 85 children were undernourished at diagnosis, 44(52%) moved to the well-nourished group and 5(6%) to the overweight/obese group. Of the 96 children who were well-nourished at diagnosis, 17(18%) moved to the overweight/obese group while 51(53%) remained in the same group. It was noted that the change in BMI in these patients was more towards the beginning of maintenance phase of chemotherapy. Various reports have shown similar trend, but significant weight gain was noted at various phases of treatment by others.

In a study by Withycomb et al [10] the author has looked at the weight patterns in children enrolled on CCG 1961 and found that successful treatment of higher risk childhood ALL was associated with excess weight gain from the beginning of maintenance therapy

through the end of the study. By the end of treatment 23% of patients were obese, compared to 14% at diagnosis.

Esbenshade et al[39] found increased in BMI from induction to consolidation, then a fall at the start of DI and a rise in the early part of maintenance. It is important to serially monitor nutritional status of children for close monitoring and for necessary intervention.

Zhang et al[38] published a similar study done on 83 children. This was a retrospective cohort of 83 children diagnosed to have ALL between 1985-2010.BMI was assessed at different time points at diagnosis, end of induction, end of consolidation, very 6 months during treatment and yearly for up to 5 years post treatment. At diagnosis, 21% were overweight/obese, by the end of treatment and 5 years post-treatment, approximately 40% were overweight or obese. The mean BMI z-score increased significantly during induction ($P < 0.0001$). It increased again during the first 6 months of maintenance ($P < 0.01$). The study shows that high BMI z-score at diagnosis was associated with increased risk of being overweight/obese at treatment completion (OR = 2.9, 95% CI: 1.6-5.1). Weight gain during treatment was associated with being overweight/obese 5 years post-treatment (OR = 3.8, 95% CI: 1.1-12)

When we compared nutritional status of children at the end of treatment with that at annual follow up for the next 5 years, there was a significant increase in the number of obese/overweight children ($p<0.05$) from 7% to 35%. There was also a significant reduction in number of under nourished from diagnosis (44%) compared to 5 years post treatment (15%)(Table 26 and Fig 12).Various other studies have followed children from diagnosis and found there was increased prevalence of obesity on follow up after end of treatment (21-25).However the sample size and the duration of follow up differed in each group.

.

Impact of Nutritional Status on response to treatment and outcome

Several authors have found a significant difference in response to treatment, complications and overall survival between children in various nutritional groups (1-6, 14). The various outcomes parameters that were compared in our study were early response (day 8 blast count), day 14 bone marrow, bone marrow remission at the end of induction, febrile neutropenia episodes, relapse and death.

Begum et al [2] showed that number of days required to achieve induction remission in under nourished children was longer than the well- nourished group 39±0.72 Vs 31.63±0.17 $p<0.04$. Rot et al [4] showed that the incidence of febrile neutropenia was significantly higher in the severely malnourished group mean being 3.8 Vs 1.42 $p <0.001$. Mendizabal et al [1]showed that the relapses were more in the Bone marrow in undernourished than the well-nourished group which was 56% Vs 7% $p < 0.0001$. Similarly study by Buttirini et al [6] shows that relapse rate was higher in obese compared to non -obese children 26±2 Vs 20±0.6 ($p =0.02$).Arangure et al[14] showed that death during initial phase of treatment was 2.6 times higher in malnourished than well nourished.

In our study, on univariant analysis of response to prednisolone, day 14 bone marrow and end of induction bone marrow status, we did not find any difference between the thee nutritional groups (tables 27, 28 &29) Similarly, there was no significant difference in complications such as febrile neutropenia, relapse or death between the groups. When we compared the number of children died in well nourished vs not well nourished, there seem to be a trend towards higher mortality in the non-well nourished group (66% vs 43%). The number of children in our study was less for multivariant analysis.

Screening for metabolic syndrome in children who had completed treatment and reviewed during the study period

Of the 195 children who successfully completed treatment for ALL, 114 were followed up in the outpatient clinic with respect to their nutritional status. Those who were overweight or obese were screened for various components of the metabolic syndrome. There were 78 boys and 36 girls in the group. Most of the children belonged to the age group of 1-5 years.

The mean age at diagnosis of ALL was 5.8 years (range 11 months to 14.3 years) and these children were reviewed at a mean period of 2.4 years (range 3 months to 9 years) after completion of treatment.

At follow up 71% of the children were well nourished while 4% were undernourished. Thirty out of the 114 children were overweight/obese. Thus the prevalence of obesity in this study was 26.3%. Most of the earlier studies have reported a 40-50% prevalence of obesity in children over a 5 year period after completion of ALL treatment (ref 17-20,38)

It was interesting to compare the pattern of weight gain at follow up with the nutritional status at diagnosis and treatment completion. At diagnosis, 49% of children were undernourished. This group steadily gained weight with treatment and by follow up only 4% children remained undernourished. Similarly there was steady increase in BMI centile in the well nourished group from 51% at diagnosis to 81% at follow up. Those who were overweight at diagnosis remained the same. Other groups also have reported similar observations (38,39).In their study Zhang et al[38] observed a close association between high BMI at diagnosis and an increased risk of being overweight /obese at treatment completion. However in our study only 6% of the cohort were overweight/obese at diagnosis. Zhang et al[38] also reported an increased risk of obesity post-treatment in those with greater weight gain

during treatment. Our results also show similar findings with most of the increments in BMI occurring during treatment and no significant change in BMI from completion of treatment to follow up.(Table 26,p value <0.005,as in figure 18)

Esbenshade et al[39] observed an increase in BMI during the induction phase of chemotherapy with its return to baseline values after induction followed by a steady increase over the subsequent phases of treatment . Majority of the children in our study gained weight steadily particularly during induction and delayed intensification phase.

Of the 114 children on follow up, 30 were overweight/obese. There were 22 boys and 8 girls in this group and their mean age at follow up was 10.3 years (range 6 - 15 years). Fourteen children were aged 6-10 year s and majority (24) were pre-pubertal. The mean duration between completion of treatment and follow up was 2.1 years (range-3 months to 9 year) . Mean BMI was 24.1kg/m^2 (range 19.2 to 32.8).

Analysis of the pattern of weight gain in these children also showed a very clear trend of steady weight gain early on in the treatment phase. Thus the prevalence of obesity increased exponentially from 20% at diagnosis to 73% at the beginning of maintenance phase and 93% by the end of treatment (Table 45 & Figure 19), Six children of this group who were undernourished at diagnosis gained weight steadily and all but one moved into the overweight category by the beginning of maintenance phase. Those in the overweight/obese category at diagnosis remained so till follow up. Similar findings were also reported by Withycombe et al [10]wherein children who were obese at diagnosis had high BMI centile throughout treatment.

Both extremes of weight (under-nourished and obese) are associated with poorer treatment outcome. Mejia et al[14] reported a 2.6 times increased risk of mortality during initial phase of treatment in the malnourished group as compared to the well -nourished group. Likewise Mendizabal et al reported disease free survival of 83% in children who were well

nourished at diagnosis as compared to 37% in those who were malnourished at diagnosis(1). They also reported higher bone marrow relapse rates in the malnourished group (56% Vs 7% ($p< 0.0001$). On the other hand in a large cohort of 4260 children treated for ALL, Butturini et al[6] reported lower 5 year event free survival as well as higher relapse rate in the obese as compared to the non-obese children aged above 10 years.

Excessive weight gain in children treated for ALL is also multifactorial. The factors implicated in increased weight gain include cranial irradiation (especially dose≥ 18Gy), steroid use, growth hormone deficiency, chemo related complications and lifestyle changes. The role of leptin as well as premature adiposity rebound have also been documented in the mechanism of obesity.

In our study, only 6 children received cranial irradiation.. In contrast to other studies 29-31, there was no correlation between cranial irradiation and obesity in our study. This may be due to the limited sample size.

Maximum dose of daily steroids is given during the induction and delayed intensification phase of ALL therapy. In addition children tend to be sedentary during the initial phases of treatment. These factors are likely to have contributed significantly to excessive weight gain early on during treatment. Thus five out of the six undernourished children in our study had become overweight by the completion of delayed intensification phase. In addition lifestyle (diet & physical activity) has a major role in obesity. Post-treatment it is common for parents to be overprotective and restrict children's outdoor activities. They also tend to over feed their children using high calorie food supplements. Although we did not have detailed dietary history or physical activity details during our analysis these factors also may have contributed to excessive weight gain during and after treatment.

Growth hormone deficiency primarily affects linear growth causing a steady decrease in height velocity.83% of children in our study had their current height centile appropriate to or higher than the target height. Therefore it is unlikely that growth hormone deficiency contributed to the excessive weight gain in our cohort. The exponential increase in BMI is likely to have occurred between diagnosis and the beginning of maintenance phase. It is important to identify and modify factors that predispose to obesity during this phase of treatment.

Overweight/obese children in our study were also screened for various risk factors for metabolic syndrome. 90% of the obese children had waist circumference> 75th centile.. Waist circumference is is an indirect marker of abdominal obesity and is increasingly becoming an essential anthropometry in all obesity screening in the community. In an elegant study published by Kurian R et al[41] providing reference values for waist circumference in urban Indian children, the authors suggest that the 75th percentile of waist circumference may be used as an "action point" to identify obesity and initiate early intervention.

In our study cohort, 13% (4/30) had hypertension (BP> 95th centile). In addition 10% (3/ 30) of children had SBP and DBP above the 90th centile for age. Esbenshade et al[39] reported a high prevalence of hypertension during ALL treatment (.41.5% systolic hypertension and 24% with diastolic hypertension). There was also high prevalence of pre-hypertension. Although there was no significant hypertension in our cohort.it is important to follow them long term preferably using ambulatory blood pressure monitor. The excursions of blood pressure as well as absence of nocturnal dip are known to be associated with long term morbidity rather than blood pressure reading at one point of time. 6 children in our cohort had glucose/insulin ratio < 5 suggestive of some degree of insulin resistance, interestingly, four of them were pre-pubertal. The prevalence of dyslipidaemia was 27%(8/30) % and 7%(2/30) abnormal glycosylated haemoglobin. levels. There was no correlation

between waist circumference and other parameters such as fasting lipids, blood sugar, glucose/insulin ratio and parental BMI in our study. Absence of significant metabolic abnormalities is most likely due to the limited sample size and the younger age of our study cohort (<16 years).

Thus it is clear that excessive weight at diagnosis or excessive weight gain during treatment are unlikely to be reversed. As age advances the risk of metabolic syndrome becomes higher in those who are obese. All children in our follow-up group were under 15 years of age. Insulin resistance which is the primary metabolic abnormality in all the components of metabolic syndrome takes several years to manifest as clinical diseases such as type2 diabetes, hypertension etc. Therefore these children need long term follow up. Obesity is the most important environmental factor which amplifies insulin resistance. Simple measures such as measuring waist circumference in the clinic may go a long way in identifying children at risk for overweight. Early intervention includes recommendation of lifestyle changes in families with obese children.

One of the major limitations of our study was small sample size. In addition, considering the fact that Indian children may develop metabolic abnormalities at much lower BMI levels as compared to the rest of the world, we do not have metabolic data on the 84 children who were not obese at follow-up.

SUMMARY

SUMMARY

- 241 children treated for Acute Lymphoblastic Leukaemia (ALL) were included in this study on longitudinal assessment of nutritional status from diagnosis, through treatment and post treatment period using BMI charts.

- At diagnosis, 44% of children were under nourished, 47 % were well nourished and 9% were overweight/ obese. At end of treatment 13% were undernourished and 29% were obese. While there was a significant reduction in the number of children in the under nourished group, the proportion of obese children increased significantly from 7% at diagnosis to 29% at the end of treatment. This was statistically significant($p<0.05$)

- The impact of nutritional status on treatment response and outcome did not show statistical significance.

- 114 children were reviewed during this study period; 30(26%) overweight/obese children were identified. Only 20 % of this group was obese at diagnosis, which increased to 73% at the beginning of maintenance and 93% by the end of treatment. Six children in this group moved from under nourished at diagnosis to overweight end of treatment. This group was further screened for metabolic syndrome. The prevalence of hypertension was 13%, dyslipidaemia was 27% and glucose intolerance was 7% in the above study group.

CONCLUSIONS &

RECOMMENDATIONS

CONCLUSIONS & RECOMMENDATIONS

Nutritional status of children treated for ALL change from diagnosis, through treatment and post treatment period. In our study, it was encouraging to note that the prevalence of under nutrition reduced considerably as they went through treatment. It was also interesting to find that a significant proportion of well-nourished children became obese by the end of their treatment. In this group of obese/overweight children many had hypertension, dyslipidaemia and glucose intolerance.

Therefore, we recommend that nutritional status of children on treatment for acute lymphoblastic leukaemia be monitored closely during and after treatment. Appropriate and timely intervention should be implemented to provide good quality life for them. Early signs of metabolic syndrome should be addressed and lifestyle modification should be suggested. Nutritional interventions should be an integral part of "Fit-for-life" programs for children with cancer.

LIMITATIONS

LIMITATIONS

- This study included only a third of our patients with ALL, due to short duration of time available for the study. Therefore the sample size required for comparison of various outcome parameters between different nutritional groups could not be done.

- Clinical and biochemical profile of non-obese/overweight children were not included for comparison.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Lobato-Mendizabal E, Ruiz Arguelles GJ, Marin Lopez A. Leukemia and Nutrition.I: Malnutrition is an adverse prognostic factor in the outcome of treatment of patients with standard–risk acute lymphoblastic leukemia. Leuk Res 1989; 13(10):899-906.

2. Begum M, Jahan S, Tawfique M et al. Outcome of induction of remission in undernourished children with acute lymphoblastic leukemia. Mymensingh Med J 2012 Oct;21(4) :691-5.

3.Viana MB, Murao M, Ramos G.et al Malnutrition as a prognostic factor in lymphoblastic Leukemia: a multivariate analysis. Arch Dis. Child. 1994;71 (4) :304-10.

4.Roy A, Saha A, Chakraborty S,et al. Effects of pre -existing under nutrition on treatment related complications and treatment outcome in children with acute lymphoblastic leukemia. Clin cancer investig J 2013;2(2): 143-8.

5.Hafiz MG, Mannan MA .Nutritional status at initial presentation in childhood acute lymphoblastic leukemia and its effect on induction of remission.Mymensingh Mad J.2008 Ju;17

6. Butturini AM, Dorey FJ, Lange BJ, et al. Obesity and outcome in pediatric acute lymphoblastic leukemia. J Clin Oncol. 2007; 25:2063–2069.

7. Brenner H, Kaatsch P, Burkhardt-Hammer T, et al. Long-term survival of children with leukemia achieved by the end of the second millennium.Cancer 2001; 92(7):1977-83.

8. Sala A, Pencharz P, Barr RD. Children, Cancer and Nutrition – A dynamic triangle in review. Cancer 2004;100(4):677-87

9.Kumar R, Marwaha RK, Bhalla AK, et al. Protein energy malnutrition and skeletal muscle wasting in childhood acute lymphoblastic leukemia. Indian Pediatrics 2000;37:720-6.

10.Withycombe JS, Post-White JE,Meza JL, et al. Weight patterns in children with higher risk ALL: A report from the Children's Oncology Group(COG) for CCG 1961.Pediatr Blood Cancer 2009;53:1249-54.

11. Alejandra Maldonado-Alcázar, Juan Carlos Numez-Enriques, Carlos Alberto Garcia-Ruiz et al .Alterations of Nutritional Status in Childhood Acute Leukaemia. Research Unit of Clinical Epidemiology, Hospital of Pediatrics, National Medical Centre 21st Century, Mexican Institute of Social Insurance,(IMSS),Mexico City, Mexico.

12. Reilly JJ,I Odame, B E Gibson et al. Does weight for height have prognostic significance in children with acute lymphoblastic leukaemia**?** Arch Dis Child 1995; 72(1):98

13.Rogers PC. Nutritional Status As a Prognostic Indicator for Paediatric Malignancies. J Clin Oncol 2014 May 1;32 (13):1293-4

14. Mejia-Arangure JM, Fajardo-Gutierrez A, Reyes-Ruiz et al. Malnutrition in childhood lymphoblastic leukemia: a predictor of early mortality during the induction-to-remission phase of the treatment. Arch Med Res 1999 Mar-Apr;30(2):150-3

15. Orgel E, Sposto R, Malvar J et al. Impact on survival and toxicity by duration of weight extremes during treatment for pediatric acute lymphoblastic leukemia: A report from the Children's Oncology Group J Clin Oncol.2014 May 1,32(13):1331-7

16. Aldhafiri F, McColl J.H. & Reilly J.J.(2014) Prevalence of being underweight and overweight and obese at diagnosis in UK patients with childhood acute lymphoblastic leukemia 1985-2002 J Hum Nutr Diet,27,76-79

17.Love E, Schneiderman JE, Stephens D, et al. A cross sectional study of overweight in pediatric survivors of acute lymphoblastic leukemia (ALL). Pediatr Blood Cancer. 2011 Dec 15;57(7):1204-9.

18.Kourti M, Tragiannidis A, Makedou A, et al. Metabolic syndrome in children and adolescents with acute lymphoblastic leukemia after the completion of chemotherapy. J Pediatr Hematol Oncol. 2005;27:499-501.

19. Razzouk BI, Rose SR, Hongeng S, et al. Obesity in survivors of childhood acute lymphoblastic leukemia and lymphoma J Clin Oncol. 2007;25:1183-89.

20. Didi M, Didcock E, Davies H, et al. High incidence of obesity in young adults after treatment of acute lymphoblastic leukemia in childhood. J Pediatr. 1995; 127:63–67.

21. Odame I, Reilly JJ, Gibson BES, Donaldson MDC: Patterns of obesity in boys and girls after treatment for acute lymphoblastic leukaemia. Arch Dis Child 1994, 71:147-149.

22. Van Dongen-Melman JE, Hokken-Koelaga AC, Hahlen K, et al Obesity after successful treatment of ALL in childhood. Pediatr Res 1995, 38:86-90.

23. Talvensaari KK, Lanning M, Tapanainen P, Knip M: Long-term survivors of childhood cancer have an increased risk of manifesting the metabolic syndrome. J Clin Endocrinol Metab 1996, 81:3051-5.

24. Reilly JJ, Ventham JC: Risk factors for excess weight gain in children treated for acute lymphoblastic leukemia. Int J Obes Relat Metab Disord 2000, 24:1537-41.

25. Nysom K, Holm K, Michaelsen KF, Hertz H, Muller J, Molgaard C: Degree of fatness after treatment for acute lymphoblastic leukemia in childhood. JClin Endocrinol Metab 1999, 84:4591-4596.

26. Meacham LR, Gurney JG, Mertens AC, Ness KK, Sklar CA, Robison LL,Oeffinger KC: Body mass index in long-term adult survivors of childhoodcancer. A report of the childhood cancer survivor study. Cancer 2005,103:1730-1739.

27. Jarfelt M, Lannering B, Bosaeus I, Johannsson G, Bjarnason R: Body composition in young adult survivors of childhood acute lymphoblastic leukaemia. Eur J Endocrinol 2005, 153:81-9.

28. Lughetti L, Patrizia Bruzzi, Barbara Predieri et al .Obesity in patients with acute lymphoblastil leukemia in childhood .Italian Journal of Pediatrics 2012,38:4

29. Rosen GP, Nguyen HT, Shaibi GQ et al..Metabolic Syndrome in Pediatric Cancer Survivors: A Mechanistic review. Pediatr Blood Cancer 2013;60:1922–8

30. F Craig A D, Leiper, R Stanhope. Sexually dimorphic and radiation dose dependent effect of cranial irradiation on body mass index. Arch Dis Child 1999;81:500-4.

31. Khan RB, Hudson MM, Ledet DS, et al
Neurologic morbidity and quality of life in survivors of childhood acute lymphoblastic leukemia: a prospective cross-sectional study. J Cancer Surviv. 2014 Jul 10.

32. Vaisman N, Stallings VA, Chan H, Weitzman SS, Clarke R, Pencharz PB. Effect of chemotherapy on the energy and protein metabolism of children near the end of treatment for acute lymphoblastic leukemia. Am J Clin Nutr. 1993 May;57(5):679-84.

33. Floyd J,Mizra I,Sachs B et al Hepatotoxicity of chemotherapy. Semin Oncol 2006;33:50-67.

34. Co-Reyes E, Li R, Huh W, Chandra J. Malnutrition and Obesity in Pediatric Oncology Patients: Causes,Consequences, and Interventions. Pediatr Blood Cancer. 2012 Dec 15;59(7):1160-7.

35. Ross JA, Oeffinger KC, Davies SM, et al. Genetic Variation in the Leptin Receptor Gene and Obesity in Survivors of Childhood Acute Lymphoblastic Leukemia: A Report From the Childhood Cancer Survivor Study.J Clin Oncol. 2004 Sep 1;22(17):3558-62.

36. Wallace A, Tucker P, Williams D, et al. Short-term effects of prednisolone and dexamethasone on circulating concentration of leptin and sex hormone-binding globulin in children being treated for acute lymphoblastic leukaemia. Clin Endocrinol. 2003; 58:770–6.

37. Rolland-Cachera MF, Sempe M, Guillard-Bataille M: Adiposity rebound in children: a simple indicator for predicting obesity. Am J Clin Nutr 1984,34:129-35.

38. Zhang FF, Rodday AM, Kelly MJ, et al. Predictors of being overweight or obese in survivors of pediatric acute lymphoblastic leukemia (ALL).

Pediatr Blood Cancer 2014 Jan 30.

39. Esbenshade AJ, Simmons JH, Koyama T, et al. Obesity and Insulin Resistance in Pediatric Acute Lymphoblastic Leukemia Worsens During Maintenance Therapy. Pediatr Blood Cancer 2013;60(8):1287-91.

40. Taylor RW, Jones IE, Williams SM et al .Evaluation of waist circumference, waist-to-hip ratio, and the conicity index as screening tools for high trunk fat mass, as measured by dual-energy X-ray absorptiometry, in children aged 3-19 y. Am J Clin Nutr 2000:72:490-5

41. Kurian R,Thomas T,Lokesh DP et al. Waist circumference and waist for height percentiles in urban South Indian children aged 3-16 years. Indian Pediatr.2011 Oct :48(10):756-71.

42. Zhang YX,Wang. The relationship of waist circumference distribution to blood pressure levels among children and adolescents in Shandong ,China .Int.J Cardiol.2013 Sep 30;168(2):1516-20.

43.Bassali R,Waller JC, Gower B et al, Utility of waist circumference percentiles for risk evaluation in obese children.Int J Pediatr Obes 2010;5 (1):97-101.

44. Khadilkar A, Ekbote V, Chiplonkar S et al ·Waist Circumference Percentiles in 2-18 Year Old Indian Children .J Pediatr 2014;164:1358-62

45. Khan AU, Sheikh MU, Intekhab K et al. Effect of hypoproteinemia on treatment outcome in children with acute lymphoblastic leukemia. J Ayub Med Coll Abbottabad. 2006 Apr-Jun;18(2):53-6.

46. Rivera-Luna R, Olaya-Vargas A, Velásquez-Aviña M,et al .Early death in children with acute lymphoblastic leukemia: Does malnutrition play a role? Pediatric hematology and oncology 251(1):17-26.

47. Ashish Bajel, Biju George, Vikram Mathews, Auro Viswabandya,, M.L.Kavitha, Alok Srivastava, and Mammen Chandy, Treatment of Children With Acute Lymphoblastic Leukemia in India. Using a BFM Protocol Pediatr Blood Cancer 2008;51:621–25.

48. Fatima Bachir, Sanae Bennani, Ali Lahjouji, Siham Cherkaoui, M'hamed Harif Characterization of Acute Lymphoblastic Leukemia subtypes in Moroccan Children. Int. J Pediatrics 2009 ID 674801:1-7.

49. Gaynon PS, Angiolillo AL, Carroll WL et al. Long term results of the children's cancer group studies for childhood acute lymphoblastic leukemia 1983-2002: a Children's Oncology Group Report. Leukemia 2010 Feb;24(2):285-97.

50. Inamullah, Shah Taj Khan, Hameeda Qureshi , Hameeda Qureshi, Fazli Raziq Frequency of Central nervous system involvement in acute lymphoblastic leukemia at presentation. J. Med. Sci. April 2013, 21(2): 81-3.

51. Heinonen K, Rautonen J, Siimes MA, Knuutila S. Cytogenetic study of 105 children with acute lymphoblastic leukemia. Eur J Haematol. 1988 Sep;41(3):237-42.

52. Kerketta LS, Baburao V, Ghosh K. Pattern of chromosome involvement in childhood/hyperdiploid pre-B-cell acute lymphoblastic leukemia cases from India. Indian J Hum Genet 2014;20:32-6.

ANNEXURE

ANNEXURE

Treatment protocol

Proforma

Information sheet in English

Informed sheet in Tamil

Informed consent in English

IRB approval letter

Excel worksheet

Annexure 1 : Treatment protocol

Pre Induction- Day 1-7

Dexamethasone IV 6mg/m2 Day 1& 2

Prednisolone PO 60mg/m2 Day 3-7 in 2 doses

Induction : day 8-29

Protocol for ALL children for Standard risk.(SR)

Induction- Day 8 count is mandatory for all patients.

Prednisolone PO 60mg/m2 Day 8-29 & taper over 1 week

Vincristine IV 1.5mg/m2 on D 8, 15, 22, 29

Daunorubicin IV 30mg/m2 on D 8, 15, 22, 29

L-Asparaginase IM 10,000 iu /m2 x 9 doses

Methotrexate IT D 1 & 8

Consolidation

Cyclophosphamide IV 1000mg/m2 on Day 1 & 21

Cytarabine SC/IV- 75mg/m2 16 doses on days 1-4, 8-11, 15-18, 22-25

Methotrexate IT 12mgdays 1, 8, 15, 22

6Mercaptopurine PO 60mg/m2 daily for 4 weeks

Radiotherapy was started after completing Consolidation(18 Gy for those with definite CNS disease / 12Gy for those with traumatic CSF 24 Gy for overt testicular disease at diagnosis which is persisting)

Interim Maintenance

Vincristine	IV	1.5mg/m2 on day 1 & 29
Dexamethasone	PO	6mg/m2/day x 5 days week 1 &5
Methotrexate	IT	on day 1 & 29
6 Mercaptopurine	PO	75mg/m2 daily for 8 weeks
Methotrexate	PO	20mg/m2 weekly for 8 weeks on Wednesdays

Delayed Intensification

Phase 1(Reinduction)

Vincristine	IV	1.5 mg/m2 on Days 1, 8, 15
Adriamycin	IV	30mg/m2 on Days 1, 8, 15
L-Asparaginase	IM	10,000 iu /m2/d on Days 1, 4, 7, 11
Inj Methotrexate	IT	12mg on day 1 & 18
T. Dexamethasone	PO	10mg/m2 on weeks 1 &3

Phase 2(Reconsolidation)

Cyclophosphamide	IV	1000mg/m2	Day 1
Cytarabine SC/IM		75mg/m2	Day 1-4, 8-11
6-Thioguanine	PO	60mg/m2	daily for 2 weeks

Maintenance (2years for girls and 2 ½ years for boys)

Vincristine	IV	1.5mg/m2 monthly
Dexamethasone	PO	6mg/m2 for 5 days every month
Methotrexate	IT	once in 12 weeks
6 Mercaptopurine	PO	75mg/m2 daily
Methotrexate	PO	20mg/m2 weekly

ALL treatment protocol for IR & HR (Intermediate and high risk)

ALL - IR would receive two intensification blocks

ALL- HR (where BMT is not an option)

Induction	4 Drug induction as per standard protocol
Consolidation	3 drug + triple IT Methotrexate

Followed by 18Gy cranial RT / 4 courses of HD Methotrexate

Escalating Capizzi Maintenance/ 4 courses of HD Mehtotrexate

Vincristine 1.5 mg/m2 on days 2, 12, 22, 32 & 42

2.Proforma:

NAME: …….

HOSPITAL NO: ……..

DATE OF BIRTH ☐☐ ☐☐ ☐☐☐☐

SEX: (1) **Male** (2) **Female**

AGE OF DIAGNOSIS ☐ **Yrs**

DATE OF DIAGNOSIS: ☐☐ ☐☐ ☐☐☐☐

DIAGNOSIS :

1. PRE B ALL
2. T CELL ALL
3. BIPHENOTYPIC ALL
4. OTHERS

DURATION OF SYMPTOMS:

1. Days
2. Months

SYMPTOMS

1. Fever
2. Respiratory system
3. Bone Pain
4. Pallor
5. Fatigue
6. Bleeding
7. Neck Swelling
8. Abdominal distension ± Pain
9. Loss of Apetite
10. Weight Loss
11. Others

EXAMINATION

1. Pallor
2. Icterus
3. Edema
4. Bleeding Signs
5. Hepatomegaly
6. Splenomegaly

LYMPHADENOPATHY:

1. YES
2. NO

If YES :

1. Cervical
2. Axillary
3. Inguinal

INVESTIGATIONS AT DIAGNOSIS: -

Hb	-
WBC	-
PLATELETS	-
BLASTS IN THE PERIPHERY	-
BONE MARROW BLAST	-

CNS DISEASE

1. Positive
2. Negative

TESTES

1. Involved
2. Not Involved

IPT

1. PRE B ALL
2. T CELL ALL
3. BIPHENOTYPIC
4. OTHERS

RTPCR

1. Done
2. Not Done

CYTOGENETICS

1. Done → Hyperploidy
1. Done → Hypoploidy
2. Not Done

RISK STRATIFICATION:

1. Standard
2. Intermediate
3. High

TUMOUR LYSIS:

1. Present
2. Absent

DAY 8

WBC -
BLAST -
BLAST COUNT -

DAY 14

BONE MARROW BLAST -

END OF INDUCTION BONE MARROW IN

1. Remission
2. Not In Remission

NO. OF DI

1. One
2. Two

CRANIAL RT

1. Given
2. Not Given

DATE OF COMPLETION OF TREATMENT:

Details of Febrile Neutropenia requiring adneuseone

No. of Episodes

Episodes No:

Lower ANC:

No. of days Hospitalised

ANTIBIOTICS

1) 1ST LINE

2) 2ND LINE

3) HIGHER THAN 2ND LINE

4) ANTIFUNGALS

BLOOD CULTURE **Positive**

2	**Negative**

If positive name of the organism isolated _____

Any Swab Culture	1	**Positive**
If done	2	**Negative**

Episodes of Febrile Neutropenia in each phase of chemotherapy

Induction ☐ **Consolidation** ☐ **interim Maintenance** ☐

Delayed intensification ☐ **Maintenance** ☐

	At Diagnosis	At Day 1 of DI-1	At Day 1 of Maint.	End of Rx
Weight (kg)				
Height (cm)				
BMI				
BMI Centile				
<5%				
5-85%				
>85% but <95%				
>95%				
Nutritional Groups				
Under Nourished				
Well Nourished				
Overweight/Obese				

Date of completion of Rx

☐☐☐☐ ☐☐☐☐

Post Treatment HBsAg	1	**Positive**
	2	**Negative**

ECHO **EF%** _____

FS% _____

OUTCOME: Relapse

1	Yes
2	No

If YES site of relapse

	Blood
2	Bone Marrow
3	Testis
4	CNS

TIME OF RELAPSE

1	During Treatment
2	Post Treatment

2nd RELAPSE

1.	YES
2.	NO

IF 2nd RELAPSE SITE OF RELAPSE

1.	Bone Marrow
2.	Testes
3.	CNS

FOLLOW UP AFTER TREATMENT

Month/Years after completion of Rx					
Wt					
Ht					
BMI					
BMI CENTILE					
<5%					
5-85%					
>85% but <95%					

>95%					
Nutritional Groups					
Under Nourished					
Well Nourished					
Overweight/Obese					

POST TREATMENT ☐ **Months after treatment**

☐ **Years after treatment**

DEATH ☐ **1** **Yes**

☐ **2** **No**

If YES ☐ **1.** **During Treatment**

☐ **2.** **Post Treatment**

If During Treatment –phase of Rx ☐ **1** **INDUCTION**

☐ **2.** **CONSOLIDATION**

☐ **3.** **IM1**

☐ **4.** **DI1 PH1**

☐ **5.** **DI1 PH2**

☐ **6.** **IM2**

☐ **7.** **DI2 PH1**

☐ **8.** **DI2 PH2**

☐ **9.** **MAINTENANCE**

☐ **1**

SECOND MALIGNANCY **Yes**

2	**No**

PROFORMA

PART II

Last Follow-up Visit date: | | | | | | | | |

No. of months after completion of treatment _____

Weight	
Height	
BMI	

BMI PERCENTILE

<5%	
5-85%	
>85% BUT <95%	
>95%	

Waist Circumference (cm)

Blood Pressure (mm HG)

Blood Pressure >90% for height for age – Yes / No

Tanner Stage

TANNER stage	Breast / Genitalia	Pubic Hair
1.		
2.		
3.		
4.		
5.		

Acanthosis nigricans Present / Absent

Lipid profile

Total Cholesterol	
Triglyceride	
HDL	
LDL	

Fasting Blood Sugar

HbA1c

Fasting insulin level

PARENTS DATA

	Fathers Data	**Mother's Data**
Weight		
Height		
BMI		

Diet – Overeating / Normal / under –eating

Physical activity – Sedentary (TV/Indoor) / Active (outdoor/exercise)/ both

3.Information sheet in English:

PATIENT INFORMATION SHEET

This information sheet will explain to you the details regarding the present study. Kindly go through this carefully. You are free to clear your doubts before consenting to participate in this study.

TITLE OF RESEARCH:

Longitudinal assessment of nutritional status and its effects on the outcome of children completed treatment for Acute Lymphoblastic Leukemia.

PERSON CARRYING OUT RESEARCH: Dr. R. Magdalenal

I'm Dr.R.Magdalenal , a PG registrar working in the department of paediatrics , CMC Vellore. I am doing a study on the effect of nutritional status of children treated for blood cancer. Details of the study are given below. I would like you to be part of this study, but the choice is yours; you can decide not to take part in this study. I am happy to clarify your doubts, if there are any.

This study will be done in children who have completed treatment for Acute Lymphoblastic Leukaemia, a type of blood cancer. It is known from other studies that nutritional status (weight and height) at diagnosis and through treatment has an effect on the outcome. The well nourished children have better outcome than those who are under weight or over weight. We wilI collect the weight and height of your child at diagnosis and during treatment from their hospital record and look at the effect of that on their response to treatment.

Some children with leukaemia have a tendency to put on too much weight, especially after completion of treatment. It is known that if they remain over weight, they are likely to develop some complications such as high blood pressure, diabetes, high cholesterol and heart problems at an early age. It is recommended that children with overweight should be checked for these complications and appropriate measures to be taken to prevent or delay these complications. Second part of my study is to check blood pressure, blood sugar, insulin levels and cholesterol in those who are overweight. These tests have been regularly done for children during their follow up visits. 5-8ml of blood will be collected from each child to do these tests during their follow up visit. I will also be checking waist circumference of children, as it is a good indicator of obesity.

CONFIDENTIALITY:

Your name will not be mentioned anywhere neither in the data sheet nor in the final published study. Your data will bear a study number and the number will be used till analysis. The master sheet will have your study number

SHARING OF THE RESULT:

The results of research are property of Christian medical college and I'm entitled to publish it in a journal or present in a conference.

This proposal has been reviewed and approved by [IRB, Christian Medical College], which is a committee whose task it is to make sure that research participants are protected from harm. If you wish to find more about the IRB,

Contact

Research Office,

Second floor, Carman block,

Christian Medical College,

Bagayam, Vellore 632002.

Email: research@cmcvellore.ac.in, Telephone: 04162284294.

It has also been reviewed by the Ethics Review Committee CMC Vellore, which is supporting the study.

In case of doubts or questions, please contact Dr.R.Magdalenal.

Department of Paediatrics, Christian Medical College and Hospital, Vellore.

Ph.No.9443040411

PART II: Certificate of Consent

I have read the foregoing information/ it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

If illiterate Thumb impression (R / L)

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____ and **Thumb print of**

participant

Signature of witness _____

Date _____

Day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

1. Data regarding weight and height will be taken from OP chart.

2. .Blood test -for lipid levels ,fasting insulin and blood glucose

3. Waist circumference measurement.

4. Participation is voluntary and cost of blood test will be borne by the research fund.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent-Dr.R.Magdalenal

Signature of Researcher /person taking the consent_____

Date _____

.

4.Tamil information sheet:

நோயாளி தகவல் தாள்:

இந்த தகவல் தாள் உங்களுக்கு, தற்போதைய ஆய்வு குறித்த விவரங்களை விளக்கும். தயவுசெய்து படித்து இந்த ஆய்வில் பங்கேற்க ஒப்புதல் முன்பாக, உங்கள் சந்தேகங்களை போக்கவும்.

ஆராய்ச்சி தலைப்பு:.

ரத்த பூற்று நோயால் பாதிக்கப்பட்டு, குணப்படுத்தபட்ட குழந்தைகளின் ஊட்டச்சத்து நிலையும் அதன் விளைவுகளின் நீண்ட மதிபீடு.

ஆராய்ச்சி நடத்தும் மருத்துவர்: மகதலேனால்.

என்னுடைய பெயர் மகதலேனால். நான் கிரிஸ்துவர் மருத்துவ கல்லூரி வேலை செய்து வருகிறேன். நான் ரத்த பூற்று நோயால் பாதிக்கப்பட்டு, குணப்படுத்தபட்ட குழந்தைகளின் ஊட்டச்சத்து நிலை மற்றும் மருத்துவ முறையின் விளைவுகள் குறித்த ஆய்வு செய்து வருகிறேன்.

நீங்கள் இந்த ஆய்வின் ஒரு பகுதியாக இருக்க முடியும். இந்த ஆய்வில் பங்கேற்க வேண்டாம் என முடிவு செய்ய முடியும். உங்கள் சந்தேகங்களை தெளிவுபடுத்த சந்தோஷமாக விரும்புகிறேன்.

ரத்த பூற்று நோயால் பாதிக்கப்பட்டு, குணப்படுத்தபட்ட குழந்தைகளின் ஆய்வு இது. ரத்த பூற்று நோய் கண்டறிதலின்போது இருந்த ஊட்டச்சத்து நிலை (எடை மற்றும் உயரம்), சிகிச்சையின் விளைவை பாதிக்கும் என

மற்ற ஆய்வுகளில் இருந்து அறியப்படுகிறது.

நன்கு ஊட்டச்சத்து உள்ள குழந்தைகள் எடை கீழ் அல்லது மேல் எடை உள்ள குழந்தைகளை விட மருத்துவ முறையின் விளைவுகளில் நன்றாக உள்ளார்கள்.

உங்கள் குழந்தையின் எடை மற்றும் உயரம் பற்றிய விவரங்களை அவர்கள் மருத்துவமனையில் பதிவுச்சான்றிலிருந்து, ரத்த பூற்று நோய் கண்டறிதலின்போது மற்றும் சிகிச்சையின் போது ஆய்வு செய்து, அவர்களின் சிகிச்சையின் விளைவை கண்டறியமுடியும்

ரத்த பூற்று நோயால் பாதிக்கப்பட்ட சில குழந்தைகள் குறிப்பாக சிகிச்சை முடிந்த பிறகு, அதிக எடை போட வாய்ப்பு உண்டு. அதிக எடை இருந்தால், அவர்கள் ஒரு ஆரம்ப வயதில் உயர் இரத்த அழுத்தம், நீரிழிவு, உயர் கொழுப்பு மற்றும் இதய பிரச்சினைகள் சில சிக்கல்கள் ஏற்படும் சாத்தியம் என்று அறியப்படுகிறது. அவ்வாறு அதிக எடை கொண்ட குழந்தைகள் இந்த சிக்கல்களிள் இருந்து தடுக்க அல்லது தாமதப்படுத்த எடுக்கப்படும் பொருத்தமான நடவடிக்கைகளை சரிபார்க்கப்பட வேண்டும் என்று பரிந்துரைக்கப்படுகிறது.

. இரண்டாம் பகுதியாக, அதிக எடையுள்ள குழந்தைகள் இரத்த அழுத்தம், இரத்த சர்க்கரை, இன்சுலின் அளவு மற்றும் கொழுப்பு உரிய சோதனை செய்யப்படும். குழந்தைகளின் இரத்தம் 5 8ml சோதனைக்கு எடுக்கப்படும் குழந்தைகள் இடுப்பு சுற்றளவு சோதனை. செய்யப்படும்

இரகசியத்தன்மை:

உங்களுடைய பெயர் தரவு தாள் அல்லது இறுதி வெளியிடப்பட்ட ஆய்வில் எங்குமே குறிப்பிடப்படாது. உங்கள் தரவு ஒரு ஆய்வு எண் சுமக்கும் மற்றும் எண் பகுப்பாய்வு வரை பயன்படுத்தப்படும்.

ஆய்வின் முடிவு பகிர்வு:

ஆய்வின் முடிவுகள் கிரிஸ்துவர் மருத்துவ கல்லூரிக்கு உரிய சொத்து மற்றும் எனக்கு ஒரு பத்திரிகை அல்லது ஒரு மாநாட்டில் கலந்து அதை வெளியிட உரிமை இருக்கிறது.

முகவரி:

ஆராய்ச்சி அலுவலகம்,

கிரிஸ்துவர் மருத்துவ கல்லூரி,

பாகாயம்,

வேலூர்.

: 04162284294.

5. English consent form:

Informed Consent Form for Subjects

Informed Consent form to participate in a research study

Study Title: Longitudinal assessment of nutritional status and its effects on the outcome of children completed treatment for Acute Lymphoblastic Leukemia.

Study Number: _____

Subject's Initials: _____ Subject's Name:

_____

Date of Birth / Age: _____

(Subject's parent)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions.

(ii) I understand that my baby's participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at the health records of my baby both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access.

However, I understand that identity of my baby will not be revealed in any information released to third parties or published.

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).

(v) I agree to take part in the above study.

(vi) I am aware of the Audio-visual recording of the Informed Consent.

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: _____ Signature:

Or Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____